CAVELIER ABOGADOS COLO-1 5439-841-003-0 ID-164928

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S U P E T III111 1 Sam

R I N E N D F N C I A I

Fecha: 2010-02-03 17:03:29 Dep. 2020 DIR.NUEVASCR Tr, 11 PATENTEIY Eve: 378 FASENACIONALI Act. 411 PRESENTACION Folios: 845
FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL....
SOLICITUD DE:

1 EI Patente de InvencOn. 0 Patente de Modelo de Utilidad.
1 CapItulo I. 0 CapItulo ii.

Nombre: BIOVAIL LABORATORIES (D INTERNATIONAL SRL

SOLICITANTE Sociedad constituida existente bajo las
leyes de Barbados. IDENTIFICACION

Direcciôn: Chelston Park, Building 2, C.C. 0 NIT 0
Collymore Rock, C.E. 0 Otro 0
St. Michael BB14018
Barbados Cual

NUmero Domicilio: CoUymore Rock,
St. Michael,
Barbados

Q Nombre: LUZ CLEMENCIA DE PAEZ IDENTIFICACION

Direcciôn: Carrera 4, No. 72-35 C. C. EI NIT 0
REPRESENTANTE

TelØfono: 3473611
C. E. Otro
OAPODERADO

Fax’ 211 8650

E-mail: clientes(cavelier.com Cual
Domicilio: Bogota, Colombia. NUmero 35.456.344 T.P 23.555
1. Robert Parry WILLIAMS 2. Peter Harris SILVERSTONE
4 Rivendell, Ballybrew, 175 Osland Drive,
Enniskerry, Co. Edmonton,
INVENTOR (ES) Wicklow;.’ Alberta T6R 2A1,
(72) Irlanda Canada

0 PCT (86)

Solicitud Internacional No. PCT/EP2008/060361 Fecha. 06 de aqosto de 2008
Publicaciori Internacional No WO 2009/019294 A9 Fecha 12 de febrero de 2009

TItulo (54)
6 BROMHIDRATO DE BUPROPION V APLICACIONES TERAPEUTICAS

Clasificación Internacional (51)A61K 031/137

Prioridad (33) Pals de Origeni (32)Fecha 1(31) NCimero de Solicitud

07deagostode2007 I SIII 11/834,848
Comprobante de de 2009
Comprobante de pago No.: Fecha: enero
Comprobante pago enero

CAVELIER ABOGADOS COLO-I 5439-841-003-0

Anexos:

ID-164928

9

01

EJ Comprobante de pago de la tasa de presentación de la solicitud por,$ 554.000.00.
EI Comprobante de pago por 9 reivindicaciones adicionales despuØs de la dØcima reivindicaciôn
por $234.000oo.

Ei Documento que acredita la existencia y represeritación legal cuando el solicitante sea persona
jurIdica.

1I Poderes, Si fuere el caso.
0 Documento de cesión del inventor al solicitante o a su causante.
0 Declaraciones.
EI Copia de la solicitud internacional. (Resumen, descripciOn, reivindicaciones, dibujos)
E1 Traducción de la solicitud internacional al castellano. (Resumen, descripciOn, reivindicaciones,
dibujos)

0 Copia del examen preliminar efectuado por la IPEA.
0 Traducción del examen prelimiriar efectuado por la IPEA.
0 De ser el caso, copia del contrato de
0 De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos
tradicionales de las comunidades indIgenas.

O De ser el caso, certificado de depOsito del material biologico.
0 Arte final l2xl2
0 De ser el caso, informaciôn sobre otras solicitudes de patente o tItulos obtenidos en el
extranjero por el mismo titular o su causante, relacioriadas parcial o totalmente con la invenciOn
de esta solicitud.

EI Otros: VER HOJA DE DOCUMENTOS ANEXOS

CAVELIER ABOGADOS COLO-1 5439-841-003-0

FIGURA CARACTERISTICA

ID-164928

12

fl

Solicito la concesiôn de la patente,
NOMBRE:

FIRMA:

LUZ CLEMENCIA DE PAEZ

C.C. 35.456.344 de Usaun T.P. 23.555

CAVELIER ABOGADOS COLa-15439-841-003-0 JD-164928

DOCUMENTOSANEXOS

PublicaciOn Internacional WO 2009/019294 A9

DescripciOn:
PÆginas341 en el idioma original PÆginas354 en espanol
Reivindicaciones: Nümero (s) i.
Figuras: NUmero (s) 54

2. j19 Forma PCTIISAI2I0. Informe de Büsqueda Internacional.

3. Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE

INTERNACIONAL

BlOVAIL LABORATORIES INTERNATIONAL SRL

CERTIFICATE

I, ARLENE L. FONG of Biovail Laboratories International SRL (the Society) of Cheiston Park, Collymore Rock, St. Michael, Barbados do hereby declare that I am a Manager and Secretary of(the Society) and as such, am authorised to make this statement on the Society’s behalf. I certify that the Society is a Corporation legally incorporated under the laws of Barbados for the purpose of owning and operating a pharmaceutical business and that the Society is engaged in activities compatible with its corporate purposes.

DATED at St. Michael, Barbados this day ofMay, 2006.

I: Arlene L. Font
Manager and Seer

BARBADOS

NOTARIAL CERTIFICATE

I, GODFREY WINSTON BINDS Notary Public in and for the Island of Barbados do hereby CERTIFY that on the day and the date hereofpersonally came and appeared before me a female person who identified herselfto be ARLENE L. FONG the person named and described in the foregoing Certificate and in my presence did sign seal and deliver the same as and for her free and voluntary act and deed and that she did present the Certificate of Organisation ofBiovail Laboratories International SRL which attests to the above-noted statement.

GIVEN under my hand and Notarial Seal of Office this 5 day ofA1, 2006

Notary Public in and for t ’1512
I &r’),L
DEPUTY REGISTRAR ANDS
1A NOTARY PUBLIC IN
AND EQRBAABADOS

NOT’s"-, M...0

- I

AV1LIER 179 - ABOGADOS

EDIFICIO SISKI
CARRERA 4a N’72-35
BOGOTA. a COLOMBIA

REPRESENTACION V PODER

f?l: ’ 1 Representación y Poder con autenticación notarial y Apostilie para patentes, modelos de utilidad, diseflos industriales, marcas de fÆbrica, nombres comerciales,
ensefias, nombres de domnio, lemas comerciales,
licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTATION AND POWER OF
ATTORNEY

Yo (nosotros), abajo firmado (s)/J (we), the undersigned

BlOVAIL LABORATORIES INTERNATIONAL SRL

dornicihado (s) en/of Chelston Park, Building 2,

Coflymore Rock, St.Michael, Barbados, West Indies

pot el presente nombramos a EMILIO }?ERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados on la Can-era 4a N° 12-35, Bogota, Colombia, en obedecimiento a lo dispuesto en ci parÆgrafo lo del Articulo 543 del Código de Comercio, ci primero corno principal y los demÆs como supientes, on so orden, como mis (nuestros) representantes on todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reetnpiazarÆa] principal en caso de ausencia o impedimento temporal o definitivo de aquØl. La misma regla se apiicarÆcuando ci segundo representante suplente haya de reemplazar al primero, o ci tercero al segundo. En tales casos, ci representante principal, o ci primero, o segundo suplente, en su caso, o ambos, declararÆn so intencidn de no ejercer la representacidn mediante declaracidn autenticada pot Notario Pdblico en Colombia, o per Notario u otto Funcionario Ptiblico, o Cónsul de Colombia, en ci extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, ci siguiente toniarÆ su lugar. Cuando cesare Ia ausencia o impedimento del representante principal, o de su pritnern o segundo suplentes, en su caso, podrÆn ejercer la representacidn, en su orden, uno u otros segdn ci caso, asumiØndola pot ci solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación pot ci primero, segundo o tercer suplente en su caso.

AdemÆs, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protecciOn de rni (nuestra) propiedad industrial y contra Ia competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdiccidn, especialmente ante las del orden administrativo, contencioso-administrativo yjudicial, asi como los tribun -

' CAVELIER ABOGADOS

WPPODEOI-179 (MINUTA 12 I].2.5)

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and GERMAN CAVELIER, tpa. 832, domiciled at Carrera 4a N 72.35, Bogota, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in theirturn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation. can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

In addition, we grant a Power of Attorney in favor of the abovenamed attorneys_at_law, so that they may obtain the protection of my (our) ’industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative in all

’to lo concerniente a los siguientes asuntos: a) Obtención de patentes de invenciOn, modelos de utilidad y diseuios industriales; ci registro de marcas de fÆbrica,colectivas, defensivas, de servicio, lemas cc,merciales, nombres comerciales, enseftas, nombres de clorninio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voiwitaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protecci6n del consumidor, oposiciones u observaciones, caucelación administrativa y judicial, nulidad, medidas cautelares, concesiôn de licencias, ’a tutela, Ia protecciuin de secretos industriales, y en general los juicios civiles, penales, adniinistrativos o contenciosoadministrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos prornuevan. Y para que en todos ins asuntos arriba determinados, puedan sustitujr este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, eancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting oflicenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (Us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a
power of attorney.

Dado y firmado boy/Given and signed this 5"R

en/in 13916i&i4 k’(gAb

por/byAK 6 4jCs-

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F i rma/Signatu reON

(IN

' CAVELIER ABOGADOS
WPPODEOI-179 (MINUTA 12.1.1.2.5)

CERTIFICACLON NOTARIAL (SOCIEDAI)

El infrascrito Notario Certifica: Que la firma que antecede de

- es autthtica; que el signatario desempefla actualmente el cargo de

de la compaiiIa BlOVAIL LABORATORIES INTERNATIONAL SRI
sociedad que actualmente existe y est. organizada de acuerdo a]as leyes de
Barbados

que Ta dirección de dicha compaæia es
Chelston Park, Building 2,
Collymore Rock, St.Michael,
Barbados, West Indies
y que el signatario tiene facultad para otorgar este
documento.
Todos los hechos anteriores le constan por haber examinado
. los documentos respectivos y de todo ello da fe.
Dado y firmado en
Ciudad
Pals

Hoy del rnes de de 200

NOTARIAL CERTIFICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature of

is authentic, that the signatory currently acts in the position of

ofthe company BlOVAIL LABORATORIES INTERNATIONAL SRI
a company currently existing and organized under the laws of

Barbados
that the address is

Cheiston Park, Building 2,
Collymore Rock, St.Michael,
Barbados, West Indies
and that the signatory has the power to grant this document.

The Notary Public is aware and attests to the above facts upon examination ofthe corresponding documents.
Given and signed in
City
Country
This day of 200 -

APOSTILLE

(Convention de La Haye du 5 octobre 1961)
1. Country:
This public document
2. has been signed by:
3. acting in the capacity of:
4. bears the seal/stamp of:

' CAVELIER ABOGADOS
WPPOIDEOI-179 (MINUTA 12.1.1.2.5)

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Thereby cet:ify that theabov&.rnent1oned Society.thØ Articics:ofOrgaæisationOfwhich are attached, was organised under the Societies with Restricted Liability Act of Barbados,

I9ENE 2010

2, Proposed name or nanesInorderôflpreference
(a) BIOVAiL LABORATORIES INTERNATIONAL SRI.
(b).
(c

3. Maihtype.ofbuiæesstheSodety.-Carriesonqrproposes tocarryon:
(a) An International Society in accordance with the Societies with Restricted Liability Act
1995-7. ..

. (b) The Society Is formed forthe purposes of owning and operating a pharmaceutical business,
In accordance with the Societies with Restricted liability Act 1995-7.
(c)

4. Derivation. of name
Parent Company

S. First name avallableto.be reserved: Yes 0 ’No [I

6. Name Is for:
Organisatlon

7 Itfor a change of name, state.presentname of Society-
Not Applicable

For Ministry use onIyr-

Name reserved until (spAci jiaLe) F5r Director

3 See attached letter if name is not reserved

Date received: Request received by:

24- - 2j

2 9 ENE 2010

CONSENT

BIOVAIL L0R4rr(IES TNCOBYORATED, amalgamated under the

Companies Act Cap.. 308 of,the laws: of Barbados on the 16th day. ofMarch, 2004,
hereby consents to the Use: of the, -name.. BlOVAIL LABORATORIES IN. ERNAflONAL.:.SRL ad 4ny variation, thereofac.ptab1e to the Registrar by the proposed body. eoorate Articles of Organization for which are being flied by Liza A. Bartidyal-Sodha. and.others

IN WITNESS WHEREOF BIOVML LABORATORIES

INCORPORATED has:heretlnto executed.thiseonsent;underthehands ofits proper Officer.in that behalf.

Dated at BridgetowijBarbados this 2l day ofDecember, 2004.

CONSENT

JilO/AIL HOLDINGS LTD, iiierporaed. undr:te.Cornpa&eS.Act Cap

308 of the laws of aarbados on the 23rd day of Xanuary 2001, hereby consents to the
use of the tathe BIOVAIL LAIORATOBJES INTEN.ATIONAL SRL and any variatrnn thereof acceptable, to the Registrar by the proposed body corporate Articles of Organization for which are being fi1edbyLza A. EarriayaI-Sodha and others.

IN WITNESS WH1EREO1? BIOVAIL HOLDINCS LTD has hereunto executed this consent under the hands ofits proper Qf1cQr u that beha1

Dated at Bridgetown, Barbados this 21. day of Decthb. 2004

S.
Date

LDmt.21,2004 Liza’k Harridyal-Sodha Orgàniser

For Ministry use.ofly
Society. Number. U$ D Filed: 2 oa

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RESTRLO car TT

NTaLuALRCLR1

2. NÆtice is given that.on the day of If the follo1æg person(s) was
director(s)

3. Notice.isyentht.On the day of the following person(s) ceasCdto hold office as
manager(i)

4. The maflagersôfthe,sOdeWars of this date are

Name Residential M.diess Occupation

Eugene P1. MelnVk Beach House, Crane, St Philip, Barbados .Business. Executve

Arlene L Fong 2 South Point View, Enterprise,
:Ctu-lst Church, Barbados

Business Executive

Paul W Haddy 826 Graere Hafl Park,
Christ Church, Barbados.

Buslnes xecubve.

Date A Signature 4 litle

-

I, LIZA A..HARRIDYALSODHA
Name of;AttrnØy

of Suite 130, The Savannah Business Centre, Hastings, Christ Church, Barbados
Business Address

hereby consent to act as the Registered Agent for BIOVAII. LABORATORIES INTERNATIONAL SRL

Know all men by these present that BXOVAIL LABORATORIES INTERNATIONAL $RL of Suite 130, The Savannah Business Centre, Hastings, Christ Church, Barbados (hereinafter called the ’Society") hereby appoints Liza ’A. Harridyal-Sodha as its Registered Agent of Suite 130, The Savannah Business Centre, Hastings, Christ Church, Barbados to act as such, and as..such to be sued, plead and be Impleaded In.,any:Court in Barbados, and generally on behalf of the Society within Barbados to accept service of process and to receive all lawful notices and, for the purposes of the Society to doF all the acts a:nd to execute all deed andother instruments reiatlhg to the matters within the scope of this appointment It Is hereby, declared that service of process in respect of suits and proceedings against the Society and to lawful notices on the.Registered Agent ii!be binding on the Society for alt purposes.

C

1. Name.’of’Sodety’

BIOVAILLABO’RTORES.INTERNATIONALSRL

Society.Nurnber tQ

2. The purpose for whid’the Society wag formed
The Society is formed for the purposes of owning and operating a pharmaceutical business, in accordance, with the SociEties With Restricted. Liability ’Act..t995-7.

3. ThedurätlQri of the Sodety(Shall not: exceed 50 years).

FIftV (50)’years4.
The registered office of the Society In Barbados
Building NO. 2, Cheiston Park,.Collymore;ROck, St Michael, Barbados

S The name and address of the S clety5 agent in Barbados
Liza A. Harridyal-Sodha
Suite130, The Savannah.BuslnessCentn,.HastIngs,.Chrit Church,. Barbados

6 The classes and any maximum number of quotas that the Society is authorized to Issue
The Sócletyls’ authorized to iSue an unlimited number ôf4uótas designatad.aS:COn’mOnQuOtaS.

7. Restrictionon.transfer of quotas
The.annexed.Schedule I islncorpontediætothis form.

8. ResUidion if any on business the Society, may carry,
The Society shall not engage in any business other than the business of an Znternatlonal Society
with Restricted Liability asdefinad in Societies with Restricted Llabftity, ACt 2995-7

:9.. Other provisions Ifany
Theannexed SchedulelIts Incorporated Into this form.

10. signatories: Date: December 21,.. 2004

Address Si urc

[Name Liza A..:Harridyal-Sodha ’=0..liii,

For Miflistry use only
Society Number: Filed: L4 r’

.Section (5)

SCHEDULE ORGANISATION

Name of Society No

BIOVAIL L.ABORATORXES:XNTERNATIONAL SRL

7 Restrictions on TrahsferofQuotas:

In accordance with the Societies with Restricted Liability Act, 1995-7 (the "SRL Act"), a transferee shall not become a member of, or participate in the management of the business affairs of the Society unless all the Members unanimously consent in writing to the transfer. No transfer of quotas in the capital of the Society shall be registered without the approval of the Board of Managers of the Society or of a committee of the Board of Managers of the Society evidenced by resolution. The Board of Managers shall decline to register the transfer of any, quotas which Is not authorized by the Articles of the SRL Act or which 15 not effected in the manner prescribed by the Articles or the SRL Act.

Name Address Signature

Uza A. Harndyal-Sodha Gunste, Brittons Hill, f jj_

Form I

Name of Society Society No. BIOVAIL LABORATORI ES7 INTERNATIONAL SRL

9. Otherprovisions ifany:

This International Society with Restricted Liability may not:

A. 1. acquire or hold land in Barbados, other than land required for business
held by way of lease or tenancy agreement for a term not exceeding
the period fixed in the Articles for the duration of the Society or such
shorter period as circumstances require;
2. transact business with any person resident in Barbados;
3. take deposits from any, person in contravention of thel Financial
Institutions Act 1996-16.

B. Any invitation to the public to subscribe for quotas or debentures of the
Society is prohibited.

Name Address Signature

Liza A. Harridyal-Sodtia Gunsite, Brittons Hill,

I

TRADtJCCION OFICIAL 150/2006 DE UN DOCUMENTO ESCRITO EN INGLES Y EN ESPA1OL DE ACUERDO CON EL CIJAL BIOVAIL LABORATORIES INTERNATIONAL SRL, EMPRESA DOMICILIADA EN CHELSTON PARK, BUILDING 2, COLLYMORE ROCK, ST. MICHAEL, BARBADOS, WEST INDIES,
OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA
831; LUZ CLEMENCIA DE PAEZ, TPA 23555 Y A GERMAN CAVELIER, TPA 832.

EXPEDIDO Y FIRMADO HOY 5 DE MAYO DE 2006 EN BRIDGETOWN, BARBADOS, POR ARLENE FONG, GERENTE Y SECRETARIA,
FORMA 2. SOCIEDAD 443
LEY DE BARBADOS SOBRE SOCIEDADES CON RESPONSABILIDAD RESTRINGIDA CERTIFICADO DE CONSTITUCION
BIOVAIL LABORATORIES INTERNATIONAL SRL

Por la presente certifico que la sociedad arriba mencionada, cuyo certificado de CONSTITUCION se adjunta, fue creada de acuerdo con la Ley de Barbados sobre socieclades con responsabilidad restringida.
Firmaclo: Registrador de asuntos societarios y propiedad inLelectual
Fecha de constitución: 21 de diciembre de 2004.
SOLICITUD DE BISQUEDA Y DE RESERVA DE NOMBRE

1. Nombre, direcciÆn yn.mero de telØfono de la persona que haga la solicitud:
LIZA A. HARRIDYAL-SODHA
THE SAVANNAH BUSINESS CENTRE
SUITE 130, HASTINGS
CHRIST CHURCH, BARBADOS
Nimero de telØfono: 246-228-9888

27’

2. Nombre o nombres propuestos en orden de preferencia 2-.
(a) BIOVAIL LABORATORIES INTERNATIONAL SRL
(b)
(c)
3. Tipos principales de negocios que la empresa realiza o se propone realizar:
(a) Una sociedad internacional de acuerdo con la Ley de sociedades con responsabilidad restringida 1995-7
(B) La sociedad estA forxnada con el objeto de poseer y operar una empresa farinacØutica de acuerdo con la Ley de sociedacles con . responsabilidad restringida 1995-7
4. Derivación del nombre: empresa matriz
5. Primer nombre disponible para reservar: (DATa EN BLANCO)
6. El nombre es para ORGANIZACION
7. En caso de que sea para cambio de nombre, –nforrnar el nombre
actual de la empresa: No se aplica
PARA USO SOLO FOR EL MINISTERIO
APROBADA.
FECHA DE RECIBO: 21 DE DICIEMBRE DE 2004.
SOLICITUD RECIBIDA POR D. BLACK.

CONSENTIMIENTO
BIOVAIL LABORATORIES INCORPORATED, fusionada de acuerdo con la ley de CompaæIas Capitulo 308 de las leycs de Barbados el 16 de marzo de 2004, por la presente consi

BIOVAIL LABORATORIES INTERNATIONAL SRL

aceptable del mismo para el registrador

corporativo. Su documento de constituciôn es rad.icado por LIZA A. HARRIDYAL-SODHA y otros.
En testimonio de 10 cual, BIOVAIL LABORATORIES INCORPORATED ha firmado este consentimiento a travØs de su funcionario adecuado.
Fechado en Bridgetown, Barbados, 21 de diciembre de 2004
BIOVAIL LABORATORIES INCORPORATED
POR ARLENE FONG, DIRECTOR.
CONSENTIMI ENTO

BIOVAIL HOLDINGS LTD, constituida de acuerdo con la ley de compafIas CapItulo 308 de las leyes de Barbados el 23 de enero de 2001, pot el presente consiente en usar el nombre BIOVAIL LABORATORIES INTERNATIONAL SRL, y cualquiex- variación del misino aceptable para el Registrador. Los Articulos de CONSTITUCIÔN son radicados par LIZA A. HARRIDYAL-SODHA y otros.
En testimonjo de lo cual, BIOVAIL HOLDINGS LTD ha firmado este consentimiento mediante el funcionario adecuado.
Fechado en Bridgetown, Barbados hay 21 de diciembre de 2004.
BIOVAIL HOLDINGS LTD.
POR: FIRMA ILEGIBLE
ARLENE FONG, DIRECTOR

LEY DE BARBADOS SOBRE EMPRESAS DE RESPONSABILIDAD RESTRINGIDA SECCIONES 23(1) Y (2)
NOTIFICACIÔN BE DIRECCIÔN [I]
NOTIFICACION BE CANBIO DE DIRECCION DE OFICINA REGISTRADA
1. NOMBRE BE LA SOCIEDAD:
BIOVAIL LABORATORIES INTERNATIONAL SRL
SOCIEDAD NIJMERO 443

2. DIRECCIÔN DE OFICINA REGISTRADA
BUILDING NO. 2, CHELSTON PARK
COLLYMORE ROCK

3. DIRECCION POSTAL
BUILDING NO. 2, CHELSTON PARK
COLLYMORE ROCK
ST. MICHAEL
BARBADOS
4. EN CASO DE TRATARSE DE CAMBIO DE DIRECCION, INFORMAR LA DIRECCION PREVIA DE LA OFICINA REGISTRADA (NO SE APLICA)

5
FECHA:
21 DE DICIEMBRE DE 2004.
FIRMA: LIZA A. HARRIDYAL-SODHA
TTIJLO: FUNDADOR
SOLO PARA USO DEL MINISTERIO
SOCIEDAD NUMERO 443
RADICADO EL 21 DE DICIEMBRE DE 2004 NOTIFICACION DE GERENTES 0
NOTIFICACION DE CANBIO DE GERENTES
1. NOMBRE DE LA SOCIEDAD
BIOVAIL LABORATORIES INTERNATIONAL SRL
SOCIEDAD NMERO 443

2 (DATOS EN BLANCO)
3. (DATOS EN BLANCO)
4. LOS GERENTES DE LA SOCIEDAD A ESTA FE

NOMBRE DIRECCION RESIDENCIAL OCIJPACION
EUGENE N. MELNYK BEACH HOUSE, CRANE, EJECUTIVO
ST PHILIP, BARBADOS
ARLENE L. FONG 2 SOUTH POINT VIEW, EJECUTIVO
ENTERPRISE, CHRIST
CHURCH, BARBADOS
PAUL W. HADDY 826 GRAEME HALL PARK EJECUTIVO
CHRIST CHURCH,
BARBADOS

FECHA: 21 DE DICIEMBRE BE 2004.
FIRMA: LIZA A. HARRIDYAL-SODHA
TITULO ORGANIZADORA

CONSENTIMIENTO PARA ACTUAR COMO AGENTE REGISTRADO

Yo, LIZA A. HARRIDYAL-SODHA, de SUITE 30, The Savannah Business
Centre, Hastings, Christ Church, Barbados, por el presente consiento en actuar como agente registrado para BIOVAIL LABORATORIES INTERNATIONAL SRL de acuerdo con el nombramiento de

agente registrado de fecha 21 de diciembre de 2004 y radicado aqul.
Fechado hoy 21 de diciembre de 2004.
Firma del agente registrado.
TESTIGO:
NOMBRE: RUTH CAMPBELL, DIRECCION LOVELL RD, M STR, ST. JOHN
OCUPACION: SECRETARIA

NOMBRAMIENTO BE AGENTE

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Por el presente se informa a quien corresponda que BIOVAIL LABORATORIES INTERNATIONAL SRL de Suite 130, The Savannah Business Centre, Hastings, Christ Church, Barbados (que a continuaciÆn liamaremos la Sociedad) por el presente nornbra a
LIZA A. HARRIDYAL-SODHA corno su agente registrado domiciliado en
SUITE 130, The Savannah Business Centre, Hastings, Christ Church, Barbados, para actuar como tal, y quien puede ser demandado, derriandar y litigar en cualquier corte de Barbados y en general a nombre de la sociedad dentro de Barbados ser notificado y en general recibir todo tipo de notificaciones jurIdicas y dentro de los objetivos de esta sociedad realizar todos los actos y firmar todos los documentos e instrumentos relacionados con los asuntos dentro del &mbito de este nombramiento. Se declara que las notificaciones con respecto a demandas y actuaciones contra la sociedad y con respecto a notificaciones jurIdicas al agente registrado serÆri obligatorias para la sociedad para todo propôsito.

FECHA: 21 DE DICIEMBRE DE 2004. FIRMADO: LIZA A. HARRIDYAL-SODHA, ORGANIZADORA.

ARTftIJLOS DE CONSTITIJCIÔN
1. NOMBRE DE LA SOCIEDAD:
BIOVAIL LABORATORIES INTERNATIONAL SRL
SOCIEDAD NUMERO 443

2. El objeto social de la sociedad es
La sociedad se constituye para ser propietaria y operar una empresa farmacØutica de acuerdo con l
responsabilidad restringida 1995-7
3. La duraci6n de la sociedad serÆ por CI

I

4. La oficina registrada de la sociedad en Barbados es
Building No. 2, Cheiston Park, Collymore Rock, St. Michael, Barbados

5. El nombre y la dirección del agente de la sociedad en Barbados son los siguientes;
LIZA A. HARRIDYAL-SODHA, Suite 130, The Savannah Business Centre, Hastings, Christ Church, Barbados
6. Las clases y el nilmero mâximo de cuotas que la sociedad estÆ
autorizada a emitir
La sociedad estÆ autorizada a ernitir un nmero ilimitado de cuotas, ilamadas cuotas comuries.
7. Restricción en la transferencia de cuotas;
El Cuadro I adjunto queda incorporado a esta forma.
8. Restricciôn (de existir) relacionada con los negocios que
puede realizar la empresa
La sociedad no puede participar en ningün negocio que no sea el
de una sociedad internacional con responsabilidad restringida tal como se define en la Ley de sociedades con responsabilIdad restringida 1995-7.
9. Otras estipulaciones:
El Cuadro II anexo se incorpora a este formulario.
Fecha: 21 de diciembre de 2004
10. Signatarios:
NOMBRE DIRECCIÔN FIRMA

Liza A. Harridyal- ff6 Gunsite,
Sodha Hill, St. Michael, IIIiI

t9!i 29 ENE 2010

Barbados

PARA USO DEL MINISTERIO SOLAMENTE:

0

SOCIEDAD 443. PRESENTADO EL 21 DE DICIEMBRE DE 2004
SELLO: REGISTRADO: FIRMA D -B. FECHA 21 DE DICIEMBRE DE 2004 OFICINA DE PROPIEDAD INTELECTUAL Y ASUNTOS SOCIETARIOS
ANEXO I A LOS ARTfCULOS DE CONSTITTJCION
NOMBRE DE LA SOCIEDAD:
BIOVAIL LABORATORIES INTERNATIONAL SRI
SOCIEDAD NUMERO 443
7. RESTRICCIONES A LA TP1NSFERENCIA DE CUOTAS:

De acuerdo con la ley de sociedades con responsabilidad restringida, 1995-7 (Ley SRL) un beneficiario de transferencia de cuotas no se volverâ miembro, ni participarâ en la administraciôn de los asuntos ernpresariales de la sociedad a menos que todos los miembros expresen unÆnimemente su consentimiento con la transferencia. Ninguna transferencia de cuotas en el capital de la sociedad se registrar& sin contar con la aprobaciôn de la junta de gerentes de la sociedad o de un comitØ de la junta de gerentes de la sociedad evidenciada POT resolución. La junta de gerentes rechazarÆ el registro de transferencia de cuotas que no estØ autorizado por los articulos de la Ley SRL o que no se haya efectuado en la forma estipulada por los artIculos de la Ley SRI.
NOMBRE DIRECCION FIRMA
LIZA A. HARRIDYAL- #6 GUNSITE, BRITTONS ILEGIBLE
SODHA HILL, ST. MICHAEL,
BARBADOS

ANEXO II A LOS ARTICULOS
NOM2RE DE LA SOCIEDAD: BIOVAIL LABORA
SOCIEDAD 443

- 9 xrl??

9. Otras estipulaciones:
Esta sociedad internacional de responsabilidad restringida no
podrÆ:
A. 1. Adquirir o poseer tierras en Barbados, diferentes de los
terrenos requeridos para negocios pot via de convenio de
aiqulier financiero o arrendamiento pot un periodo no mayor al periodo fij ado en los articulos para la duración de la sociedad o por un periodo menor de acuerdo a lo que requieran las circunstancias;
2. Realizar negocios con cualguier persona residente en Barbados;
3. Recibir depósitos de cualguier persona, contraviniendo la ley de Instituciones Financieras 1996-16.
B. Est& prohibida cualquier invitaciôn al piblico a suscribir cuotas 0 instrumentos.
Nombre Dirección Firma
LIZA A. HARRIDYAL- t6 GUNSITE, BRITTONS ILEGIBLE
SODHA HILL, ST. MICHAEL,
BARBADOS

BIOVAIL LABORATORIES INTERNATIONAL SRL
CERTIFICACION

Yo, ARLENE L. FONG, de Biovail Laboratories International SRL La sociedad) de Cheiston Park, Coil
Barbados pot la presente declaro que s
la sociedad y que en mi calidad de t
realizar esta declaración a nombre de
sociedad es una sociedad legairnente c
de Barbados con el objeto de pose

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farmacØutica y que ella participa en actividades compatibles con
su objeto social.
Fechado en St. Michael, Barbados, hoy 5 de mayo de 2006.
Firmado: ARLENE L. FONG, gerente y secretario
SELLO: BIOVAIL LABORATORIES INTERNATIONAL, SRL.
CERTIFICACION NOTARIAL

Yo, GODFREY WINSTON HINDS, notario p6blico para la isla de Barbados certifico que en la fecha y hora del presente compareció personalmente ante ml una persona de sexo femenino quien se identificó como ARLENE L. FONG, la persona nombrada y descrita en el certificado precedente y en mi presencia fIrmó y entregö el misrno como un acto de su propia voluntad y libre albedrlo y que ella presentc5 el certificado de constitución de Biovail Laboratories International SRL, que da fe de la at irrnaciôn anterior.

Expedido con mi firma y el sello notarial oficial hoy 5 de mayo de 2006.
FIRMA ILEGIBLE
NOTARIO PUBLICO PAPA LA ISLA DE BARBADOS
SELLO: REGISTPADOR SUPLENTE Y COMO TAL NOTARIO PtBLICO PARk

40 BARBADOS.

OFICINA DE PROPIEDAD INTELECTUAL Y ASUNTOS SOCIETARIOS.
APOSTILLA

(CONVENCI6N DE LA HAYA DEL 5 DE OCTUBRE DE 1961)
1. PAlS: BARBADOS
Este docurnento püblico
2. ha sido firmado por GODFREY WINS
3. quien actia en su calidad de RE(EN SIJ CALIDAD NOTARIO PUBLICO PAPA

4. y lieva el sello/estampilla de NOTARIO PUELICO DE BARBADOS -

CERTIFICADO

5. en BRIDGETOWN, BARBADOS 6. el 8 de mayo de

2006

7. por HUGHLAND ST CLAIR ALLMAN, JEFE DE PROT000LO ENCARGADO
8. Certificadonmero 657/2006
9. SELLO: MINISTERIO DE ASUNTOS EXTERIORES, BARBADOS:
10. Firma: (ILEGIBLE)
COLO- 15366-706-001-3
WPCLO02G ID 7834

Bogota, 13 de junio de 2006.

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(75) Inventors/Applicants (for US only): WILLIAMS, Robert Parry [lB/fE]; Rivendell, Ballybrew, Ifnniskeiry, Co. Wicklow (IE). S1LVERSTONE, Peter Harris [CA/CA]; 175 Osland Drive, Edmonton, Alberta, Canada T6R 2A1 (US).

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(54) Title: BUPROPION I-IYDROEROMDE AND THERAPEUTIC APPLICATIONS

(57) Abstract: Bupropion hydrobromide forniulations as well as their use for the treatment of conditions is described.

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TITLE OF, THE INVENTION
BUPROPION BYDR.OBR.OMIDE AND THERAPEUTIC APPLICATIONS

RELATED APPLICATIONS
5 ThiS application claims priority to U.S. Application Serial No. 11/834,848, filed August 7,
2007. U.S. Application Serial No. 11/834,848 is a continuation-in-part ofU.S. Application Serial No. 11/751,768, filed May 22, 2007, now pending; and a continuation-in-part ofU.S. Application Serial No. 11/755,946 filed on 4ay 31, 2007, both ofwhich are continuations of U.S. Application Serial No. 11/475,252, filed June 27, 2006, now U.S. 7,241,805; and claims
10 priority to U.S. Provisional Application Serial No. 60/693,906 filed June 27, 2005. All of
U.S. Application Serial No. 11/751,768, U.S. Application Serial No. 11/755,946, U.S.
7,241,805, and U.S. Provisional Application Serial No. 60/693,906 are incorporated herein by reference.

iS FIELD OF THE INVENTION
The present invention relates to bupropion bydrobromide and bupropion hydrobromide formulations as well as their use for the treatment ofconditions (e.g. major depressive
disorder, bipolar depression mood disorder, other mood disorder, anxiety disorders,
generalized anxiety disorder, panic disorder, post-traumatic-stress disorder, nicotine
20 addiction, obesity, attention-deficit hyperactivity disorder, restless legs syndrome, sexual
dystlinclion, and seasonal affective disorders)

BACKGROUND

Bupropion is a known antidepressant. The neurochemical mechanism ofthe antidepressant
25 effect ofbupropion Is not well known. Bupropion affects chemicals within the brain that
nerves use to send messages to each other. These chemical messengers are called neurotransmitters. The neurotransmitters that are released by nerves are taken up again by
the nerves that release them for reuse (this is referred to as reuptake). Many skilled artisans believe that depression is caused by an imbalance among the amounts ofneurotransmitters
30, that are released. Bupropion Is a selective catecholamine (dopamine and norepiriephrine)
reuptake inhibitor, and works by inhibiting the reuptake ofthe neurotransmitters dopaininc
and norepinephrinc, an action which results in more dopamine and norepinephrine made available to transmit messages to other nerves. It has a small effect, if any, on the serotonin reuptake mechanism. Accordingly, bupropion is unique in that its major effect is on

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dopamine, an effect which is not shared by selective serotonin re-uptake inhibitors (SSRTs), e.g. paroxetine (PAXILfi), fluoxctine (PROZACfi), sertraline (ZOLOFTfi) or the tricyclic antidepressants or TCAs, e.g. amitriptyline (ELAVILfi), imipramine (TOFRAINILfi), desipramine (NORPRAMJNfi).

Bupropion can also be used to treat other conditions, non-limiting examples ofwhich include nicotine addition (e.g. smoking cessation), weight gain (e.g. obesity), Parkinson’s disease,
and seasonal affective disorder.

10 Bupropion hydrochloride is commercially available as an immediate release form
(WELLBUTR1Nfi), a sustained release form (WELLBUTR1Nfi SR and ZYBANfi), and an extended release form ((WELLBUTRTNfi XL). Both WELLBUTRINfi SR and ZYBANfi
are chemically and pharmaceutically identical. WELLBUTRINfi, WELLBUTR1Nfi SR and WELLBUTRINfi XL are used clinically for the management ofmajor depressive disorder,
15 bipolar depression mood disorder, other mood disorder, anxiety disorders, generalized
anxiety disorder, panic disorder, post-traumatic stress disorder, and seasonal affective
disorders, and have been approved for use in the treatment ofmajor depressive disorder. ZYBANfi has been approved as an aid to patients wanting to quit smoking.
WELLBUTRINfi, the immediate release formulation of bupropion, is dosed three times a
20 day, suitably with 6 or more hours in between doses. For patients requiring more than 300
mg bupropion a day, each dose is prescribed not to exceed 150 mg. This requires
administration ofthe tablets at least 4 times a day with at least 4 hours in between doses. The immediate release formulation results in more than. a 75% release ofthe bupropion into the dissolution media in 45 minutes. The sustained release products are dosed twice daily, and
25 the extended release products are dosed once daily.

Certain advantages exist in using bupropion for the treatment of diseases and conditions. For example, bupropion does not inhibit monoamine oxidase, and does not significantly block the re-uptake ofserotonin, unlike other neuronal monoamine reuptake inhibitors. Administration
30 of bupropion can thus avoid or lessen many adverse effects commonly associated with other
antidepressants such as tricyclic agents and monoamine oxidase inhibitors.

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One of the known major side effects of bupropion is the incidence ofseizures (e.g. grand-mal epileptic seizures), which is known to be strongly associated with the dose strength of the bupropion. For example, with WBLLBUTRINfi at the originally recommended dosage (400-600 mg) the incidence of seizures in those treated with the drug was found to be significantly, greater than other antidepressants, and so in 1986 the drug was removed from the market. It
was shown that the risk ofseizures increased significantly between the 450 mg/day dosage
and the 600 mg/day dosage. As a result, bupropion was re-introduced into the market in 1989 with the maximum dose of 450 mg/day. However, it has been documented that seizures
occur in patients taking bupropion not only in overdose but also in doses considered to be
10 therapeutic (i.e. 450 mg/day or less) [Pesola & Avasarala, Bupropion seizures proportion
among new-onset generalized seizures and drug related seizures presenting to an emergency department, J. Emerg.Med. 2002, 22, 235-239.] The high concentrations of bupTopion.
needed for efficacy (e.g. antidepressant efficacy) establish a high floor concentration, and
thus sets the stage for a narrow therapeutic index, in light ofits concentration-dependent risk
15 of causing seizures. [Preskorn S., Bupropion: What Mechanism ofAction? J. Practical
Psychiatry and Behavioral, Health, Jan. 2000, 272-276.]

Bupropion is known to lower the seizure threshold, and has been cited as one ofthe leading
causes of drug related seizures [third behind cocaine intoxication and benzodiazepine
20 withdrawal seizures - Davidson J., Seizures and Bupropion: A Review, J. Clin.Psychiatry,
1989, 50, 256-61.]. Bupropion alone or in combination with other medications, is known to
induce seizures in some patients with no prior record ofseizure activity. It is not uncommon

46 for patients to receive treatment with other antidepressant and/or atypical antipsychotic
medications in combination with bupropion. As such, there is a need to manage, reduce, or
25 eliminate the incidences ofseizures resulting from bupropion administration, whether
administered alone or in combination with other medications prone to lower the seizure
threshold. Bupropion has also been known to produce seizures in combination with non-
prescription (recreational) drugs such as cocaine and alcohol.

30 The selection of a suitable salt for a drug candidate is recognized as an important step in the
preclinical phase of drug development. Changing the salt form of a drug is a recognized
means ofmodifying its chemical and biological properties without modifying its structure.
The choice of a particular salt form can have a profound effect on the physicochemical

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properties ofthe drug (e.g. dissolution rate, solubility, stability, and hygroscopicity). Substitution of one salt form of a drug for another can alter therapeutic efficacy, safety and/or quality, which are critical for the optimal formulation ofthe dosage form and large-scale manufacturing. However, as yet there is no reliable way ofpredicting exactly what effect changing the salt form of an active drug will have on its biological activity. Furthermore,
even after many salts ofthe same basic agent have been prepared, no efficient screening techniques exist to facilitate selection ofthe salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles. In short, there is no known reliable way ofpredicting the influence of a particular salt species on the behavior ofthe parent compound
10 in dosage forms. [Berge et al., Pharmaceutical Salts, Journal Pharm, Sci., 1977, Vol.66, No. 1;
Verbeeck et al. Generic substitution: The use ofmedicinal products containing different salts
and implications for safety and efficacy, EP Journal Pharm. Sci, 28, 2006, 1-6.] A decision to change the salt form at a later stage introduces the need to repeat toxicological, formulation
and stability tests, with obvious implications for the overall development and production time
15 for the new pharmaceutical product.

According to the CASfi ("Chemical Abstracts Registry") Database, as ofthe date ofthis
application, the only other salts of bupropion that have been previously reported are the
hydrochloride (HC1), (2Z)-2-butenedioate, (2E)-2-butenedioate, methane sulfonate, formic
20 acid, 2-hydroxy-1,2,3-propanetricarboxylate, phosphate and trifluoromethanesulfonate salts.

Sodiuri bromide and potassium bromide are salts that have been widely used as an
. anticonvulsant and a sedative iirthe late 19th and early 20th centuries. Its action is due to the
bromide ion. As ofthe date ofthis application, bromide has not been approved by the US
25 Food and Drug Administration (FDA) for use in humans to control seizures. However, in
Germany it continues to be approved for use as an antiepileptic drug for humans, particularly
children and adolescents (sold under the brand name DIBRO-BE MONOfi). The indications
include severe forms of generalized tonic-clonic seizures, early-childhood-related Grand-
Mal-seizures, and also severe myoclonic seizures during childhood. One tablet contains a
30 therapeutic dose of 850 mg of potassium bromide. Bromide was the first drug found to be
effective for the treatment of epilepsy in humans. Bromide has also been used as a veterinary drug, e.g. as an antiepileptic medication for dogs and cats.

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Recommended therapeutic dose levels of bromide for treating epilepsy have been reported.
For adults, a reported usual dose ranges from 3-6 grams/day [Niederrneyer E., ed. Beuzodiazepines and other antiepileptic drugs, In: The epilepsies: Diagnosis and
management, Baltimore: Urban & Schwarzenberg, 1990, 311-2; Ryan and Baumann,- aumaun;
5 Bromides in Epilepsy Treatment, Pediatr Neruol, 1999, 21; 523-528.]. For children under 6
years of age, dose levels of 600-1800 mg/day have been recommended in two to three doses. For children over 6 years of age, it has been recommended that 300 mg to 1 gram be given three times daily. [Dreifuss F.E. and Bertram D.H., Bromide therapy for intractable seizures, Epilepsia, 1986, 27; 593.; Ryan and Baumann; Bromides in Epilepsy Treatment, Pediatr
10 Neruol, 1999, 21; 523-528.1. The ED50 (minimum effective dose required to produce a
desired effect in 50% oftest population) for sodium bromide against chemically-induced

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seizures (induced by pentylenetetrazole) in mice has been reported to be 910 mg/kg [J,S.
Grewal et at., Journal ofPharmacology and Expt’l Therapeutics, 1954, Vol. 112, Issue 1, 109-115.]

Bromide was the principal anticonvulsant of choice until the introduction ofPhenobarbital in
1912 and other safer anticonvulsants. It was subsequently discovered that the known
therapeutic dose levels ofbromide induced bromism and a number of other significant toxic effects. The known therapeutic index is very small for bromide. As with other
20 anticonvulsants, sometimes even therapeutic doses give rise to intoxication. Often
indistinguishable from expected’ side-effects, these toxic effects can include: bromism (i.e. central nervous system reactions reaching from somnolence to coma, cachexia, exicosis, lobs ofreflexes or pathologic reflexes, clonic seizures, tremor, ataxia, loss of neural sensitivity, paresis, papillar edema ofthe eyes, abnormal speech, cerebral edema, frank delirium,
25 aggressivity, psychoses); loss of appetite; nausealemesis; lethargy; propensity to sleep during
the daytime; depression; loss of concentration and memory; confusion; headache; and skin diseases such as acne-form dermatitis.

Bromide’s precise mechanism of action is unknown. The pharmacological mechanism of
30 bupropion-induced seizures and the usefulness of antiepileptic drugs (e.g. bromide) in
treating such seizures have not been established. There is limited knowledge about the effectiveness of antiepileptic drugs in bupropion-induced seizures in mice {P.Tutka et al., Epilepsy Research 64, 2005, 13-22.1, and nothing is known about the effectiveness of

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bromide in controlling bupropion-induced seizures. While no formal studies have been carried out to determine the therapeutic dose ranges for the effectiveness of bromide against bupropion-induced seizures, the therapeutic dose ranges for the effectiveness ofbromide against other known seizures are known. For example, the therapeutic dose level for bromide against pentytenetetrazole-induced seizures is known to be 910 mg/kg [M, S. Grewal et al., Journal ofPharmacology And Experimental Therapeutics, Vol. 112, Issue 1, 109-115, 1954].
For a number of other anti-epileptic drugs (e.g. clonazepam, vigabatrin, etosuximide,
vaiproate), the therapeutic dose levels that are required for the treatment of bupropion-
induced seizures are comparable to the dose levels that are required for the treatment of
10 pentylenetetrazole-induced seizures in mice. [P. Tutka et al. Epilepsy Research 64 (2005) 13-
22; J.J. Luszczki,, 2005, 30, 958-973; J.A. Armijo et al. Pharmacological Res. 2005, 51, 489-496; K.K. Borowicz et al. Epilepsia, 2004, 45(10), 1176-1183; S.J. Czuczwar et al., Polish Journal of Pharmacology, 2003, 55, 363-370; P. Tutka et al., J. Neural Transmission, 2002,
109, 455-466; K.K.Borowicz et al. European Neuropsychopharmacology 2004, 14, 77-85;
15 and K.K.Borowicz et al., Polish Journal of Pharmacology, 2004, 56, 187-193.]

There remains a need for a bupropion composition that can be used for the treatment and/or prevention of a condition (e.g. major depressive disorder and nicotine addiction) in subjects that can benefit from bupropion administration, and that can provide fewer incidences of
20 and/or reduce the severity ofseizures associated with the administration of bupropion, as
compared to known bupropion compositions.

The development of a stable, once daily modified-release bupropion fonnulation comprising safe levels ofthe bupropion hydrobromide salt; that provides for the reduction of incidences
25 and/or reduction ofthe severity ofbupropion-induced seizures as compared to an otherwise
similar or identical composition containing an equivalent molar amount ofbupropion hydrochloride; would be an advance in the art.

DESCRIPTION

30 Certain embodiments ofthe present invention relate to a bupropion composition that
comprises a safe and pharmaceutically effective amount of bupropion hydrobromide; wherein
the composition unexpectedly provides for fewer incidences ofseizures and/or less severe

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seizures associated with the administration of bupropion than an otherwise similar or identical composition containing an equivalent molar amount of bupropion hydrochloride.

Certain embodiments ofthe invention relate to a bupropion composition that comprises a safe and pharmaceutically effective amount ofbupropion hydrobromide and at least one pharmaceutically acceptable excipient; wherein administration of an amount ofthe bupropion hydrobromide to a first rat unexpectedly results in less incidences of and/or reduces the
severity ofbupropion-induced seizures when compared to incidences ofbupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion
10 hydrochloride to a second rat; and wherein the incidences of and/or severity of bupropion-
induced seizures are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode.

Certain embodiments ofthe present invention relate to a bupropion composition that
15 comprises a safe and pharmaceutically effective amount of bupropion hydrobromide; wherein
said composition unexpectedly provides for fewer incidences ofseizures and/or less severe seizures associated with the administration of bupropion, and is more stable, than an
otherwise similar or identical composition containing an equivalent molar amount of
bupropion hydrochloride. In particular, such a bupropion hydrobromide composition is more
20 stable than an otherwise similar or identical composition containing an equivalent molar
amount of bupropion hydrochloride under certain storage conditions, (for example when
stored for 3 months or 6 months at 40 degrees C and 75% relative humidity) as evidenced by
a reduced amount of at least one moiety (e.g. degradation product) that is characteristic of bupropion degradation and/or a reduced fluctuation or reduction in potency after being stored
25 under accelerated storage conditions (for example after storage for 3 months or 6 months),
and/or by a reduced fluctuation in the in-vitro dissolution profile in at least one dissolution medium over a 24 hour period.

Certain embodiments ofthe present invention relate to methods ofreducing incidences of
30 bupropion-induced seizures and/or reducing the severity of bupropion induced seizures
comprising administering a safe and pharmaceutically effective amount of bupropion hydrobromide to a subject in need of bupropion administration, wherein said incidences of and/or severity ofbupropion-induced seizures resulting from the administration of bupropion

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hydrobromide is less than the incidences of arid/or severity of bupropion-induced seizures resulting from the administration of an equivalent molar amount of bupropion hydrochloride.

Certain embodiments ofthe present invention relate to methods oftreating a condition comprising administering a safe and effective amount of bupropion hydrobromide to a
subject in need ofbupropion administration, wherein the bupropion hydrobromide provides
for fewer incidences of bupropion-induced seizures than an equivalent molar amount of bupropion hydrochloride.

10 Certain embodiments ofthe present invention relate to methods oftreating condition

15

comprising administering a safe and effective amount of bupropion hydrobromide to a
subject in need of bupropion administration, wherein the bupropion hydrobromide provides
for fewer incidences of bupropion-induced seizures and/or reduces the severity of such
seizures than an equivalent molar amount of bupropion hydrochloride.

As shown herein below, it is demonstrated that bupropion hydrobromide has a lower
propensity to induce seizures and/or reduce the severity of bupropion induced seizures when compared to bupropion hydrochloride. This allows one to reduce the incidences ofsuch seizures, reduce the severity ofthe seizures, treat subjects who would otherwise not be
20 candidates for bupropion therapy because oftheir risk for seizure induction, and/or to treat a
subject with even higher doses of bupropion than would be possible and safe with bupropion hydrochloride.

Certain embodiments ofthe present invention relate to methods oftreating a condition
25 comprising administering a composition containing a safe and effective amount ofbupropion
hydrobromide to a subject in need of bupropion administration, wherein the bupropion hydrobromide provides for fewer incidences of bupropion-induced seizures than an
equivalent molar amount of bupropion hydrochloride.

30 Certain embodiments ofthe present invention relate to a method oftreating a subject at risk
ofbupropion-induced seizures in need of such treatment by administering a safe and effective amount of bupropion hydrobromide to the subject

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Certain embodiments ofthe present invention relate to the use of bupropion hydrobromide compositions to prepare a medicament for the treatment of one or more conditions that can benefit from the administration of bupropion, wherein the treatment allows for the reduction
or avoidance ofincidences of and/or the reduction ofthe severity of bupropion-induced
seizures as compared to an otherwise identical or similar composition containing an
equivalent molar amount of bupropion hydrochloride.

Certain embodiments ofthe present invention further contemplate a method ofpreparing a medicament for the treatment of a condition which can benefit from the administration of
10 bupropion, comprising bringing an effective amount ofbupropion hydrobromide into contact
with one or more pharmaceutically acceptable excipients.

Certain embodiments relate to the use of bromide salts to reduce the incidences and/or

severity of bupropion induced seizures, such as those seizures induced by the administration
15 ofbupropion hydrochloride.

Certain embodiments relate to compositions comprising a compound of formula I (bupropion hydrobromide):

0
Cl

H2 Br

20

HA

(I)

and pharmaceutically acceptable carriers, excipients and/or diluents; said composition having greater stability than a corresponding pharmaceutical composition comprising bupropion hydrochloride and pharmaceutically acceptable carriers, excipients and/or diluents; and
25 providing a reduction or avoidance of incidences of and/or a reduction in the severity of
bupropion-induced seizures

In certain embodiments ofthe present invention, the bupropion salt can be in the form ofits anhydrous, hydrated, and solvated forms, in the form ofprodrugs, and in the individually
30 optically active enantiomers ofthe bupropion salt, such as for example (+)-bupropion and (-)-
bupropion. Suitable pharmaceutically acceptable salts of bupropion for use in the present

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invention are more stable than bupropion hydrochloride, and provide for the reduction or avoidance of incidences ofseizures associated with the administration ofbupropion. Suitable salts of bupropion also include for example, pharmaceutically acceptable acid addition salts.
In certain embodiments, the acid addition salt of bupropion can be indirectly obtained by the separate addition of bupropion and an acid to the core formulation.

Certain embodiments ofthe present invention contemplate the use ofbupropion
hydrobromide to prepare a medicament to treat a condition which can benefit from administration ofbupropion, wherein said medicament has greater stability than a
10 corresponding medicament comprising bupropion hydrochloride, and provides for the
reduction or avoidance ofincidences of and/or the reduction in the severity ofseizures associated with the administration of bupropion.

As discussed infra and generally known in the art, appropriate dissolution medium and
15 appropriate conditions for assaying the dissolution characteristics of pharmaceutical dosage
forms such as tablets are well known in the art and are contained in the United States Pharmacopoeia and its European or Japanese counterparts, and include by way of example dissolution in USP Type 1 apparatus (Rotating Basket Method) in 900 ml water; 0.1 N HCl;
0.1N HCl + 0.1% Cetrimide; USP buffer pH 1.5; Acetate buffer pH 4.5; Phosphate Buffer pH
20 6.5; or Phosphate Buffer pH 7.4 at 75 RPM at 37 degrees C +/- 0.5 degrees C. Additionally,
other examples of appropriate dissolution media include USP-3 media and USP-3 dissolution conditions e.g,, SGF pH 1.2; Acetate buffer pH 4.5 and Phosphate Buffer pH 6.8.

Certain embodiments ofthe present invention contemplate the use ofbupropion
25 hydrobromide to produce once-daily administrable tablets or other dosage forms that are
bioequivalent to WELLBUTRINTM or ZYBANTM/WELLBT.JTRINTM SR tablets as defined
by FDA criteria when administered once daily to a subject in need thereof. In particular at
least one ofthe Tmax, Cmax, or AUC profile of certain embodiments ofthe present invention
is within 80-125% of WELLBUTRIN TM and ZYBANTM/WELLBUTRThTM when
30 administered once daily to a subject in need thereof. In certain embodiments these
formulations are also free of any significant food effect.

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Certain embodiments ofthe present invention provide bupropion hydrobromide dosage forms. (e.g. tablets) containing at least one coating (e.g. SMARTCOATTM coating) which is resistant
to dose dumping in high alcohol, (e.g., 40% ethanol), wherein the dosage forms allow for the reduction or avoidance ofincidences of and/or the reduction in the severity ofbupropion-
5 induced seizures.

Certain embodiments ofthe present invention include both oral and non-oral bupropion hydrobromide containing medicaments. For example, the invention embraces compositions suitable for oral, topical, injectable, inhalation and other modes of administration,

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Certain embodiments ofthe present invention include extended release formulations, delayed Srelease formulations, and/or enhanced absorption formulations.

In a more particular implementation of certain embodiments ofthe invention, a bupropion
15 medicament composition comprises (I) a core that includes bupropion hydrobromide, a binder
and a lubricant; and (ii) a controlled release coat substantially surrounding said core; wherein
said composition provides controlled release of said bupropion hydrobromide, and a
reduction or avoidance ofincidences of and/or a reduction in the severity of bupropion-
induced seizures. Such compositions optionally can comprise one or more additional
20 coatings surrounding the core and/or the controlled release coat such as a moisture barrier
coat, enteric coat or a coating that affects the physical integrity and/or appearance ofthe composition. The binder can be selected from known pharmaceutical binders such as
polyvinyl alcohol. The lubricant also can be selected from known pharmaceutical lubricants such as glyceryl behenate. The controlled release coat can include a water-insoluble
25 polymer, a water-soluble polymer, and optionally a plasticizer. The water-insoluble polymer
can be selected from a range ofwater insoluble polymers useful in extended release pharmaceutical compositions such as ethylcellulose. The water-soluble polymer can be
selected from a variety ofwater-soluble polymers useful in extended release pharmaceutical compositions such as polyvinylpyrrolidone. The plasticizer if present can be selected from a
30 range ofknown plasticizers such as mixtures of polyethylene glycol 4000 and dibutyl
sebacate. Certain embodiments ofthese compositions include once-daily administrable compositions that are bioequivaient to WELLBUTRINTM or ZYBANTM/ WELLBUTRINTM
SR tablets when administered once-daily to a subject in need thereof. These compositions

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may or may not exhibit a food effect. Further, certain embodiments ofthese compositions can be resistant to dose dumping in the presence of high alcohol concentrations (e.g., 40% by weight of ethanol).

In another particular implementation of certain embodiments ofthe present invention, the bupropion composition comprises (i) a core that includes bupropion hydrobromide, a binder
and a lubricant; and (ii) a controlled release coat substantially surrounding said core; wherein said controlled release coat includes an aqueous dispersion of a neutral ester copolymer
without any functional groups, a polyglycol having a melting point greater than 55°C, and
10 one or more pharmaceutically acceptable excipients, wherein said coat is coated onto said
core and cured at a temperature at least equal to or greater than the melting point ofthe polyglycol. The composition provides controlled release ofsaid bupropion hydrobromide,
and a reduction or avoidance ofincidences of bupropion-induced seizures. Optionally, this medicament can comprise one or more additional coatings surrounding the core and/or
15 controlled release coating such as a moisture barrier coat, enteric coat, coat that precludes
dose dumping in specific media such as alcohol, and/or a coating that affects the physical stability or integrity ofthe medicament and/or its physical appearance.

In a particular implementation of certain embodiments ofthe present invention, the
20 bupropion composition comprises multiparticulates.

Certain embodiments ofthe present invention include controlled release matrix tablet Sformulations.

25 Certain embodiments ofthe present invention include a bupropion composition that
comprises a second drug. The second drug (e.g. other anti-depressants, SSRJ’s, anti-anxiety agents, atypical antipsychotic drugs, medications that interact with serotonin
neurotransmission, medications that interact with norepinephrine neurotransmission,
medications that interact with dopamine neurotransmission) can be administered in
30 combination with the subject bupropion hydrobromide salt. The second drug can elicit a
synergistic benefit on bupropion efficacy as well as non-synergistic drug combinations. Non-limiting examples ofthe second drug include citalopram, escitalopram, veulafaxine,
quetiapene, buspirone and mixtures thereof.

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In accordance with one aspect of certain embodiments ofthe present invention, there is provided a controlled release composition comprising (i) a core comprising an effective amount of a bupropion hydrobromide, a binder, a lubricant; and (ii) a controlled release coat surrounding said core; and optionally (iii) a moisture barrier surrounding said controlled
release coat or the core; and; wherein the composition exhibits a dissolution profile such that
after 2 hours from about more than 0% to about 20%, including all values and subranges therebetween; preferably from about 2% to about 18%, more preferably from about 4% to
about 8%, or about 5%, ofthe bupropion hydrobromide content is released; after 4 hours
10 from about 15% to about 45%, including all values and subranges therebetween; preferably
from about 21% to about 37%, more preferably from about 28% to about 34%, or about 32%, ofthe bupropion hydrobromide content is released; after 8 hours from about 40% to about
90%, including all values and subranges therebetween, preferably from about 60% to about
85%; more preferably from about 68% to about 74%; or about 74%, of the bupropion
15 hydrobromide content is released, and after 16 hours from about 80% to about 100%
including all values and subranges therebetween, preferably not less than about 93%; more preferably not less than about 96%, still more preferably not less than about 99%, ofthe bupropion hydrobromide content is released, when using a USP apparatus design with a dissolution medium as found in the USP (e.g. USP Apparatus Type 1 at 75 rpm, 900 ml, 0. IN
20 HC1, at 37°C – 0.5°C); and wherein the bupropion hydrobromide composition is more stable
than an otherwise similar or identical composition comprising the equivalent molar amount of bupropion hydrochloride when each are stored under accelerated storage conditions (e.g.
stored for 3 months or 6 months at about 40 degrees C and at about 75% relative humidity),
and provides for the reduction or avoidance of incidences of and/or the reduction in the
25 severity of bupropion-induced seizures,

In certain embodiments the composition exhibits a dissolution profile such that after 2 hours
not more than about 0% to about 40%, including all values and subranges therebetween, of
the bupropion hydrobromide is released, after 4 hours from about 40% to about 75%,
30 including all values and subranges therebetween, ofthe bupropion hydrobromide is released,
after 8 hours not less than about 75% to about 99%, including all values and subranges therebetween, ofthe bupropion hydrobromide is released, and after 16 hours not less than
about 85% to about 100%, including all values and subranges therebetween ofthe bupropion

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hydrobromide is released, when using a USP apparatus design with a dissolution medium as found in the USP (e.g. USP Apparatus Type 1 at 75 rpm, 900 ml, 0. IN HCI, at 37°C
0.5°C).

5 Certain embodiments of the present invention include a bupropion composition that
comprises from about 50mg to about 1000mg of bupropion hydrobromide, including 75mg, 100mg, 125mg, 150mg, 174mg, 175mg, 200mg, 225mg, 250mg, 275mg, 300mg, 325mg, 348mg, 350mg, 375mg, 400mg, 425mg, 450mg, 475mg, 500mg, 5 10mg, 520mg, 522mg, 525mg, 530mg, 540mg, 550mg, 560mg, 570mg, 575mg, 580mg, 590mg, 600mg, 625mg,
10 650mg, 675mg, 700mg, 725mg, 750mg, 775mg, 800mg, 825mg, 850mg, 875mg, 900mg,
925mg, 95 0mg, 975mg, and all values and ranges therebetween. For example, certain embodiments include a composition which comprises 174mg, 348mg or 522mg ofbupropion hydrobromide per unit dose.

15 In accordance with one aspect of certain embodiments ofthe present invention, there is
provided an enhanced-absorption tablet comprising (i) a core comprising an effective amount ofbupropion hydrobromide, a binder, a lubricant; and (ii) a controlled release coat
surrounding said core; and wherein the enhanced absorption tablet exhibits a dissolution
profile such that after 2 hours, from about 0% to about 25%, preferably from about 10% to
20 about 20%, including all values and subranges therebetween ofthe bupropion hydrobromide
content is released; after 4 hours from about 25% to about 55%, preferably from about 30%
to about 50%, including all values and subranges therebetween ofthe bupropion
. hydrobromide content is released; after 8 hours from about 60% to about 99%, preferably
from about 70% to about 90%, including all values and subranges therebetween ofthe
25 bupropion hydrobromide content is released, and after 16 hours from about 70% to about
100%, preferably more than about 80%, including all values and subranges therebetween, of
the bupropion hydrobromide content is released., when using a USP apparatus design with a
dissolution medium as found in the USP (e.g. USP Apparatus Type 1 at 75 rpm, 900 ml, 0,1N
HCl, at 37°C – 0.5°C); and wherein the bupropion hydrobromide enhanced-absorption tablet
30 is more stable than an otherwise similar or identical composition comprising the equivalent
molar amount of bupropion hydrochloride when each are stored under accelerated storage conditions (e.g. stored for 3 months or 6 months at about 40 degrees C and at about 75%

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relative humidity), and provides for the reduction or avoidance of incidences of and/or the reduction in the severity of bupropion-induced seizures.

In certain embodiments the bupropion hydrobromide composition can comprise a dissolution profile such that after 2 hours from more than about 0% to about 40%, including all values
and subranges therebetween, of bupropion hydrobromide is released therefrom; after 4 hours from about 40% to about 75%, including all values and subranges therebetween, of
bupropion hydrobromide is released therefrom; after 8 hours from about 75% to about 99%, including all values and subranges therebetween, of bupropion.hydrobromide is released
10 therefrom, and after 16 hours from about 85% to about 100%, including all values and
subranges therebetween, of bupropion hydrobromide is released therefrom, when using a
USP apparatus design with a dissolution medium as found in the USP (e.g. USP Apparatus Type 1 at 75 rpm, 900 nil, OAN HCl, at 37°C – 0.51C).

15 As discussed infra, in-vitro dissolution ofbupropion from controlled or extended release
formulations according to certain embodiments ofthe invention can be determined by
methods well known to those skilled in the pharmaceutical art. Suitable methods are
contained in the United States Pharmacopoeia (USP) as well as European and Japanese counterparts ofthe USP and are exemplified infra. This includes by way of example
20 effecting dissolution in a USP 1 apparatus (Rotating Type Basket Method) in 900 ml water,

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0,1N HC1, 0.1N HCl + 0.1% Cetrirnide, USP Buffer pH 1. 5, Acetate Buffer pH 6.5 or Phosphate Buffer pH 7.4 at 75 RPM at 37 degrees C +1- 0.5 degrees C or by effecting dissolution using a USP3 dissolution medium such as SGF having a pH 1.2; acetate buffer having a pH of 4.5 or phosphate buffer having a pH of 6.8.

Stable compositions of bupropion hydrobromide (e.g compositions of bupropion hydrobromide with enhanced stability as compared to otherwise similar compositions containing bupropion hydrochloride) are known, for example, from U.S. patent number 7,241,805, the contents ofwhich are incorporated herein by reference.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow chart showing the overall process for the development ofbupropion HBr
XL tablets.

Figure 2 is a flow chart demonstrating the granulation process ofthe bupropion HBr XL and
5 EA tablets.

Figure 3 is a flow chart showing the overall tabletting process ofbupropion HBr XL.
Figure 4 is a flow chart showing the overall coating process ofbupropion HBr XL.
Figure 5 is a dissolution profile ofthe 4kp, 6-71cp and 9-1 Okp tablets, comparing the effects of hardness on dissolution in the study on Batch BUP-HBr-XL-009-5.
10 Figure 6 is a dissolution profile ofthe 348mg Bupropion HBr cores which have been
compressed using 9mm tooling in the study on Batch BTJP-HBr-XL-009-5.
Figure 7 is a dissolution profile ofthe 348mg Bupropion HBr cores which have been
compressed using 10mm tooling in the study on Batch BUIP-HBr-XL-009-5,
Figure 8 is a dissolution profile comparison ofthe 9mm and 10mm diameter 348mg
15 Bupropion HBr cores in the study on Batch BUP-HBr-XL-0095.
Figure 9 is a dissolution profile ofthe 174mg in the study on Batch BUP-HBr-XL-021-5.
Figure 10 is a dissolution profile ofBUP-HBr-XL-348mg-013-5 (28mg, 30mg, 32mg and 34
mg weight gains).
Figure 11 is a dissolution profile ofBUP-HBr-XL-348mg-0 13-5 (5mg, 6mg,. and 7mg weight
20 gains).
Figure 12 is a dissolution profile of BUP-HBr-XL-348mg-018-5 (26mg, 28mg, 30mg and 32
mg weight gains).
. Figure 13 is dissolution profile ofBUP-HBr-XL-348mg-018-5 (7mg weight gain).
Figure 14 is a dissolution profile ofBUP-HBr-XlL174mg-022-5 (22mg, 24mg, 28mg and 30
25 rug weight gains).
Figure 15 is a dissolution profile ofBtJP-HBr-XL-174mg-022-5 (5mg, 6mg, and 7mg weight
gains).
Figure 16 is a dissolution profile ofBTJP-HBr-XL-348mg-023-5 (26mg, 28mg, 30mg and
32mg weight gains).
30 Figure 17 is a dissolution profile ofBUP-HBr-XL-348mg-025-5 (26mg 28mg, 30mg, and
32mg mg weight gains).
Figure 18 is a dissolution profile of BUF-HBr-XL-348mg-025-5 (5mg, 6mg, and 7mg weight gains).

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Figure 19 is a dissolution profile ofBIJP-HBr-XL-348mg-0265 (26mg, 28mg, 30mg, and 32mg weight gains).
Figure 20 is a dissolution profile ofBUP-HBr-XL-174mg-027-5 (22mg, 241-ng, and 26mg weight gains).
Figure 21 is a dissolution profile ofI3UP-HBr-XL-174mg-027-5 (4mg, 5mg, 6mg, and 7mg weight gains).
Figure 22: Seizure activity in the hippocampus during the pre-administration phase of
30mg/kg dose test.
Figure 23: Seizure activity in the hippocampus during the pre-administration phase of
10 60mg/kg dose test.
Figure 24 A and B: Seizure activity in the hippocampus during the pre-administration phase

10 of 100mg/kg dose of bupropion hydrochloride test.
Figure 25 A and B: Seizure activity in the hippocampus during the pre-administration phase
of 1 00mg/kg dose of bupropion hydrobromide test.
15 Figure 26: Relative log number of convulsions, severe, moderate, or mild, in rats
administered bupropion hydrobromide or bupropion hydrochloride is displayed
Figures 27-32 show comparative dissolution profiles ofBupropion HBr XL tablets in various
media.

Figure 33: Mean Plasma Bupropion Concentration-Time Plot for Study B06-756PK-10 121
20 (3230)
Figure 34: Mean Plasma Hydroxybupropion Concentration-Time Plot for Study B06-756PK-
10121 (3230)

40 Figure 35: Mean Plasma Bupropion Threoamino Alcohol Concentration-Time Plot for Study
B06-756PK-10121 (3230)
25 Figure 36: Mean Plasma Bupropion Erythroamino Alcohol Concentration-Time Plot for
Study B06-756PK-10121 (3230)
Figure 37: Mean Plasma Pharmacological Activity Weighted Composite PAWC)-Time Plot
for Study B06-756PK-10121 (323 0)
Figure 38: Mean Plasma Bupropion Concentration-Time Plot for Study B06-755PK-10121
30 (3228)
Figure 39: Mean Plasma Bupropion Concentration-Time Plot for Study B06-755PK-10121 (3228) - Magnified Showing Only Datapoints From 0 - 36 Hours

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Figure 40: Mean Plasma Hydroxybupropion Concentration-Time Plot for Study B06-755PK-10121 (3228)
Figure 41: Mean Plasma Bupropion Threoamino Alcohol Concentration-Time Plot for Study B06-755PK-10121 (3228)
Figure 42: Mean Plasma Bupropion Erythroamino Alcohol Concentration-Time Plot for
Study B06-755PK-10121 (3228)
Figure 43: Mean Plasma Pharmacological Activity Weighted Composite (PAWC)-Time Plot
for Study B06-755PK-10121 (3228)
Figure 44: Mean Plasma Bupropion Concentration-Time Plot for Study B06-754PK-10121
10 (3229)
Figure 45: Mean Plasma Bupropion Concentration-Time Plot for Study B06-754PK-10121 (3229) - Magnified Showing Only Datapoints From 0 - 36 Hours
Figure 46: Mean Plasma Hydroxybupropion Concentration-Time Plot for Study B06-754PK-10121 (3229)
15 Figure 47: Mean Plasma Bupropion Threoamino Alcohol Concentration-Time Plot for Study
B06-754PK-10121 (3229)
Figure 48: Mean Plasma Bupropion Erythroamino Alcohol Concentration-Time Plot for
Study B06-754PK-10121 (3229)
Figure 49: Mean Plasma Pharmacological Activity Weighted Composite (PAWC)-Time Plot
20 for Study B06-754PK-10121 (3229)
Figure 50: Mean Plasma Bupropion Concentration-Time Plot For Study B06-802PK-10121
(AA40055)
. Figure 51: Mean Plasma Hydroxybupropion Concentration-Time Plot For Study r06-802PK-
10121 (AA40055)
25 Figure 52: Mean Plasma Bupropion Threoamino Alcohol Concentration-Time Plot For Study
B06-802PK-10121 (AA40055)
Figure 53: Mean Plasma Bupropion Erythroamino Alcohol Concentration-Time Plot
Figure 54: Mean Plasma Pharmacological Activity Weighted Composite (PAWC)-Time Plot

30 DEFINITIONS

The following definitions are provided in order to more specifically describe the invention. Otherwise all terms are to be accorded their ordinary meaning as they would be construed by
one of ordinary skill in the art, i.e. pharmaceutical drug formulations.

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The term "seizure" as used herein, means a temporary abnormal electro-physiologic
phenomena (e.g. involuntary electrical activity) of the brain, resulting in abnormal synchronization of electrical neuronal activity that can result in a wide variety of
5 manifestations, non-limiting examples ofwhich include tonic or clonic movements,
convulsions, staring, tongue biting, urination, loss of consciousness, alteration in mental state, psychic symptoms such as dØjà vu orj.amais vu, and combinations thereof. Non-limiting examples of types ofseizures include: (i) partial seizures (e.g. focal seizures) such as simple partial seizures, partial seizures (e.g. temporal lobe or psychomotor seizures) and
10 partial seizures evolving to secondarily generalized seizures; (ii) generalized seizures such as
absence petit-mal seizures), myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures (e.g. grand-mal seizures), and atonic seizures; and (iii) unclassified epileptic seizures.

15 The terms "bupropion-induced seizures" or "seizures associated with the administration of
bupropion" as used herein are used interchangeably, and mean seizures that result from the administration of bupropion or a mixture of bupropion with one or more other drugs.

The term "incidences of bupropion-induced seizures" as used herein when referring to
20 bupropion administration is defined to mean the number of bupropion-induced seizures as

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determined by behavioural observations of convulsions or other movements characteristic of
a seizure; and/or as determined by electroencephalogram ("EEG") observations of electrical activity in the brain characteristic of a seizure using cortically mounted surface electrodes
and/or hippocampally implanted depth electrodes.

The term "reducing incidences of bupropion-induced seizures", as used herein when referring
to bupropion administration, is defined to mean that the administration of bupropion hydrobromide or compositions containing bupropion hydrobromide, results in fewer
incidences of bupropion-induced seizures as compared to the administration of an equivalent
30 molar amount of bupropion hydrochloride or otherwise identical composition containing an
equivalent molar amount of bupropion hydrochloride, when exposed to identical conditions
and after identical periods oftime.

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The terms ’adverse effects associated with bupropion" or "side effects of bupropion" as used herein are used interchangeably, and mean the adverse drug reactions resulting from the administration ofbupropion or a mixture of bupropion with one or more other drugs, non-limiting examples of which include seizures, nausea, vomiting, excitement, agitation, blurred
or blurry vision, restlessness, postural tremors, hallucinations/confusional states with the potential for abuse, anxiety, insomnia, headaches and/or migraines, dry mouth, constipation, tremors, sleeping disturbances, dermatologic problems (e.g., rashes), neuropsychiatric signs
and symptoms (e.g., delusions and paranoia), weight gain, and combinations thereof.

10 The term "depression" as used herein refers to any nervous system disorder and/or mental
condition.. Non-limiting examples of "depression" include major depressive disorder, bipolar depressed mood disorder, adjustment mood disorder, and post-partum mood disorder.

The term "condition" as used herein when referring to the administration of bupropion,
15 means a condition, disease or disorder which can be treated with bupropion. Non-limiting
examples ofwhich include depression, seasonal affective disorder, anxiety disorders,
generalized anxiety disorder, social anxiety disorder, obsessive compulsive disorder, post traumatic stress disorder (PTSD), panic disorder, disorders requiring a stimulant effect, attention-deficit/hyperactivity disorder (ADHD), narcolepsy, hypersomnia, substance-abuse
20 disorders, stimulant dependence, marijuana dependence, nicotine dependence, obesity,

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female and male sexual dysfunction (e.g. premature ejaculation), premenstrual syndrome, premenstrual dysphorie disorder, neuropathic pain, fibromyalgia, diabetic neuropathy, viral infection, sleep apnea, sleep disorders, migraines, Parkinson’s disease, restless legs syndrome,
and combinations thereof.

The terms "treatment","treating" or "treat" as used herein when referring to a condition, and
as understood in the art, are defined to mean an approach for obtaining beneficial or desired results, including clinical results. "Treatment" can also mean prolonging survival of a subject as compared to the expected survival ofthe subject ifnot receiving treatment.

The terms "at risk," "patient at risk," and "a subject at risk of bupropion-induced seizures" refers to those subjects that either through existing illness, prior medical illness, past history ofseizures, prior exposure, testing, dosing or other administration of bupropion

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hydrochloride are known to have a greater propensity to have bupropion induced seizures compared to a subject who does not exhibit seizures under the same or similar conditions and/or a subject who based on a clinical evaluation ofthe subject’s health, other medications and/or treatments is expected to have a greater propensity to have bupropion induced seizure activity.

The term "palliating" as used herein when referring to a condition means that the extent
and/or undesirable clinical manifestations of a condition or disease state are lessened and/or
time course ofthe progression is slowed or lengthened, as compared to not treating the
10 condition.

The term "effective amount" or "pharmaceutically effective amount" as used herein are used interchangeably, and are defined to mean the amount or quantity ofthe active drug (e.g. bupropion hydrobromide) or polymorph or enantiomer thereof which is sufficient to elicit an
15 appreciable biological response when administered to a patient. It will be appreciated that the
precise therapeutic dose will depend on the age and condition ofthe patient and the nature of
the condition to be treated and will be at the ultimate discretion ofthe attendant physician.

The tenus "enhanced stability", "greater stability", "increased stability" or "more stable" as
20 used herein when referring to bupropion hydrobromide, can be used interchangeably in this
application, and are defined to mean that the bupropion hydrobromide or composition
containing bupropion hydrobromide, shows less degradation as determined by the formation

40 ofless of at least one degradation product characteristic of bupropion degradation, than an
equivalent molar amount of bupropion hydrochloride or an otherwise similar or identical
25 composition containing an equivalent molar amount of bupropion hydrochloride, when
exposed to similar or identical conditions. Non4irniting examples of conditions are those
described for example in US patent number 7,241,805.

The term "less degradation" as used herein when referring to bupropion hydrobromide or a
30 composition containing bupropion hydrobromide, is defined to mean any measurable
decrease in the amount of at least one bupropion degradation impurity characteristic of bupropion degradation, and/or any measurable difference in the retention of potency, relative
to an equivalent molar amount ofbupropion hydrochloride or an otherwise similar or

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identical composition containing an equivalent molar amount of bupropion hydrochloride, when exposed to similar or identical conditions.
The terms "degradation product", "bupropion degradation product", "bupropion degradation impurity" or "impurity" as used herein when referring to the degradation ofbupropion, are
5 used interchangeably and are defined to include those listed on page 281 ofthe 26th edition
ofthe USP and any other degradation product that may appear as peaks on a chromatogram during the assay that are characteristic of bupropion degradation.

The term "dissolution profile" or "release profile" as used herein are used interchangeably in
10 this application, and are defined to mean a quality control test conducted according to
instructions found in the United States Pharmacopoeia ("USP"), i.e. using a USP apparatus design with a dissolution medium as found in the USP. Dissolution tests in-vitro measure the
rate and extent of dissolution ofthe active drug in an aqueous dissolution medium. The dissolution rate or in-vitro release rates of drug from the modified release dosage forms ofthe
15 present invention can be measured using one ofmany USP apparatus designs and dissolution
media; non-limiting examples of which include a USP Type 1 apparatus design or USP Type
2 apparatus design, with a dissolution medium selected from water; 0.1N HC1; 0.1N HC1 with added Sodium Chloride (e.g. 15.7gNaCIfLitre); 0.1N HC1 with added 0.1% Cetrimide; USP Buffer pH 1.5; Acetate Buffer pH 4.5; Phosphate Buffer pH 6.5; Phosphate Buffer pH 6.8;
20 and Phosphate Buffer pH 7.4.

The term "dose dumping" as used herein in respect of "alcohol induced dose dumping" is
defined to mean the unintended premature release (in-vitro) of at least one drug from a
modified release dosage form. The term "premature release" as used herein is defined to
25 mean a release of at least one drug from a modified release dosage form in dissolution media
containing alcohol (e.g. dissolution medium containing from about 5% to about 40% ethanol) wherein the rate ofrelease is faster than the rate ofrelease of the identical drug(s) from the identical modified release dosage form in the otherwise identical dissolution media not
containing alcohol (e.g. dissolution medium containing about 100% 0.1 N HCI),
30 The terms "resistant to alcohol", "resistant to ethanol", "resistant to dose dumping", "resistant
to alcohol-induced dose dumping" and "resiting dose dumping" as used herein are used interchangeably, and are defined to mean the ability ofthe dosage form to modify release (in-vitro) ofthe at least one drug while in the presence of alcohol (e.g. from about 5% to about

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40% ethanol), such that there is not a premature release ofthe at least one drug from the modified release dosage form. For example, in certain embodiments the rate ofrelease of at least one drug from a modified release dosage form in dissolution media containing alcohol
(e.g. dissolution medium containing from about 5% to about 40% ethanol) is slower than the rate ofrelease ofthe identical drug(s) from the identical modified release dosage form in
dissolution media not containing alcohol (e.g. dissolution medium containing about 100% 0.1
N HC1).

The term "other drug" or "second drug" as used herein means a drug other than bupropion,
10 including but not limited to anti-depression agents, other neuropsychiatric drugs, atypical
antipsychotics, drug that affects central or peripheral serotonin neurotransmission, drugs that Saffect central norepinephrine neurotransmission, drugs that affect central dopamine neurotransmission, vasodilators, anti-anxiety agents, appetite modulators, sleep modulating
drugs, SSRIs, anti-viral agents, anti-pain agents, anti-migraine agents, anti-inflammatories
15 (both steroidal and non-steroidal) serotonin receptor agonists, and more particularly can
include citalopram, escitalopram, venlafaxine, clozapine, melperone, amperozide,
ioperidone, risperidone, quetiapene, olanzapine, ziprasidone, aripiprazole, reboxetine,
Viagrafi, sertraline, paroxetine, fluoxetine, gabapentin, valproic acid, aniltriptyline,
lofepraniine, fluvoxamine, hniprarnine, mirtazapine, nefazodone, nortriptyline, SAM-F,
20 buspirone, combinations thereof, and their pharmaceutically acceptable salts (e.g. the
hydrochloride salts, the hydrobromide salts, the hydroiodide salts, and the saccharinate salts),
as well as the anhydrous, hydrated, and solvated forms, polymorphs, prodrugs, and the individually optically active dnantiomers ofthe other drug.

25 The term "dosage form" as used herein is defined to mean a pharmaceutical preparation or
system in which a dose of at least one active drug is included. For example, a dosage form
can include at least one modified release dosage form, at least one osmotic dosage form, at
least one erosion modified release dosage form, at least one dissolution modified release dosage form, at least one diffusion modified release dosage form, at least one modified
30 release matrix core, at least one modified release matrix core coated with at least one
modified release coat, at least one enteric coated dosage form, at least one dosage form surrounded by at least one osmotic subcoat, capsules, minitablets, caplets, uncoated

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microparticles, microparticles coated with at least one modified release coat, or any combination thereof.

The term "medicament" as used herein refers to oral and non-oral dosage forms, including
but not limited to, all modified release dosage forms, osmosis controlled release systems, erosion controlled release systems, dissolution controlled release systems, diffusion
controlled release systems, matrix tablets, enteric coated tablets, single and double coated tablets (including the extended release and enhanced absorption tablets as described herein), capsules, minitablets, caplets, coated beads, granules, spheroids, pellets, microparticles,
10 suspensions, topicals such as transdermal and transmucosal compositions and delivery
systems (containing or not containing matrices), injectables, and inhalable compositions.

"Modified release dosage forms" as used herein is defined (e.g. as by the United States Pharmacopoeia "USP") as those whose drug release characteristics oftime course and/or
15 location are chosen to accomplish therapeutic or convenience objectives not offered by
conventional immediate release dosage forms. The rate ofrelease ofthe active drug from a modified release dosage form is controlled by features ofthe dosage form and/or in
combination with physiologic or environmental conditions rather than by physiologic or environmental conditions alone. The modified release dosage forms of certain embodiments
20 can be contrasted with conventional immediate release dosage forms which typically produce
large maximumlminimurn plasma drug concentrations (cmax!cmin) due to rapid absorption
ofthe drug into the body (i.e., in-vivo, relative to the drug’s therapeutic index; i.e., the ratio of

40 the maximum drug concentration needed to produce and maintain a desirable

pharmacological response). In conventional immediate release dosage forms, the drug
25 content is released into the gastrointestinal tract within a short period oftime, and plasma
drug levels peak shortly after dosing. The design of conventional immediate release dosage
forms is generally based on getting the fastest possible rate of drug release, and therefore
absorbed, often at the risk of creating undesirable dose related side effects. The modified
release dosage forms of certain embodiments ofthe invention, on the other hand, improve the
30 therapeutic value ofthe active drug by reducing the ratio ofthe maximum/minimum plasma
drug concentration (Cmax!Cmin) while maintaining drug plasma levels within the therapeutic window. The modified release dosage forms of certain embodiments attempt to deliver therapeutically effective amounts of bupropion hydrobromide and mixtures ofbupropion

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hydrobromide with at least one other drug as a once-daily dose so that the ratio Cmax!Crnin in the plasma at steady state is less than the therapeutic index, and to maintain drug levels at constant effective levels to provide a therapeutic benefit over a period oftime (e.g. 24-hour period). The modified release dosage forms of certain embodiments ofthe invention,
therefore, avoid large peak-to-trough fluctuations normally seen with conventional or
immediate release dosage forms and can provide a substantially flat serum concentration
curve throughout the therapeutic period. Modified-release dosage forms can be designed to provide a quick increase in the plasma concentration ofthe bupropion salt which remains. substantially constant within the therapeutic range of bupropion salt for a period oftime (e.g.
10 24-hour period). Alternatively, modified-release dosage forms can be designed to provide a
quick increase in the plasma concentration ofthe drug, which although may not remain
constant, declines at a rate such that the plasma concentration remains within the therapeutic range for a period oftime (e.g. 24-hour period). The modified release dosage forms of
certain embodiments ofthe invention can be constructed in many forms known to one of
15 ordinary skill in the drug delivery arts and described in the prior art. The USP considers that
the terms controlled release, prolonged release and sustained release are interchangeable. Accordingly, the terms "modified-release", controlled-release", "control-releasing", "rate-controlled release", "extended release", "prolonged-release", and "sustained-release" are
used interchangeably herein. For the discussion herein, the definition ofthe term "modified-
20 release" encompasses the scope ofthe defmitions for the terms "extended release",
"enhanced-absoition", "controlled release", "sustained release" and ’delayed release".

"Controlled release dosage forms", "control-releasing dosage forms", "rate-controlled release dosage forms", or dosage forms which exhibit a "controlled release" ofthe bupropion
25 hydrobromide or mixtures of bupropion hydrobromide and a second drug, as used herein are
used interchangeably in this application and are defined to mean dosage forms which release
the bupropion hydrobromide in a controlled manner per unit time in-vivo.. For example, controlled release dosage forms can be administered once daily, and release the bupropion hydrobromide at a controlled rate and provide plasma concentrations of the drug that remain
30 controlled with time within the therapeutic range ofbupropion over a 24-hour period. The
rate ofrelease ofthe bupropion hydrobromide from a controlled release dosage form is controlled by features ofthe dosage form and/or in combination with physiologic or environmental conditions rather than by physiologic or environmental conditions alone. The

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controlled release dosage forms of certain embodiments ofthe invention can be contrasted to immediate release dosage forms which typically produce large maximum minimum plasma
drug concentrations (Cmax/Cmin) due to rapid absorption ofthe drug into the body i.e., in-vivo, relative to the drug’s therapeutic index i.e., the ratio ofthe maximum drug
5 concentration needed to produce and maintain a desirable pharmacological response. In
immediate release dosage forms, the drug content is released into the gastrointestinal tract
within a short period oftime, and plasma drug levels peak shortly after dosing. The design of immediate release dosage forms is generally based on getting the fastest possible rate of drug release, and therefore absorbed,often at the risk of creating undesirable dose related side
10 effects, The controlled release dosage forms of certain embodiments ofthe invention, on the
other hand, improve the therapeutic value ofthe active drug by reducing the ratio ofthe maximum/minimum plasma drug concentration (Cmax/Cmin) while maintaining drug plasma levels within the therapeutic window. The controlled release dosage forms of certain embodiments ofthe invention attempt to deliver therapeutically effective amounts of
15 bupropion hydrobromide and/or mixtures of bupropion hydrobromide with at least one other
drug as a dose administered at least once-daily so that the ratio Cmax/Cmin in the plasma at steady state is less than the therapeutic index, and to maintain drug levels at constant effective levels to provide therapeutic benefit over a period oftime (e.g. a 24-hour period). The
controlled release dosage forms of certain embodiments ofthe invention, therefore, avoid
20 large peak-to-trough fluctuations normally seen with immediate release dosage forms and
provide a substantially flat serum concentration curve throughout the therapeutic period. The controlled release dosage forms of certain embodiments ofthe invention can be constructed
in many forms known to one of ordinary skill in the drug delivery arts and described in the
prior art such as for example, osmotic dosage forms, multiparticulate dosage forms, and
25 gastric retention dosage forms.

"Sustained-release dosage forms" or dosage forms which exhibit a"sustained-release" of bupropion hydrobromide or mixtures ofbupropion hydrobromide and a second drug as used herein is defined to mean dosageforms administered at least once-daily that provide a release
30 ofbupropion hydrobromide sufficient to provide a therapeutic dose soon after administration,
and then a gradual release over a period oftime such that the sustained-release dosage form provides a therapeutic benefit over a period oftime (e.g. a 12 -hour or 24-hour period).

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"Extended-release dosage forms" or dosage forms which exhibit an "extended release" of bupropion hydrobromide or mixtures ofbupropion hydrobromide and a second drug as used herein is defined to mean dosage forms administered at least once-daily that release the bupropion hydrobromide slowly, so that plasma concentrations ofthe bupropion
5 hydrobromide are maintained at a therapeutic level for an extendedperiod oftime such that
the extended release dosage form provides therapeutic benefit over a period oftime (e.g. 24-hour period).

"Delayed-release dosage forms" or dosage forms which exhibit a "delayed release" of
10 bupropion hydrobromide or mixtures of bupropion hydrobromide and a second drug as used
herein is defined to mean dosage forms administered at least once-daily that do not
effectively release drug immediately following administration but at a later time. Delayed-release dosage forms provide a time delay prior to the commencement of drug-absorption.
This time delay is referred to as "lag time" and should not be confused with "onset time"
15 which represents latency, that is, the time required for the drug to reach minimum effective
concentration.

"Enhanced absorption dosage forms" or dosage forms which exhibit an "enhanced
absorption" ofthe active drug as used herein is defined to mean dosage forms that when
20 exposed to like conditions, will show higher release and/or more absorption ofthe bupropion
base as compared to other dosage forms with the same or higher amount of bupropion base.
The same therapeutic effect can be achieved with less bupropion base in the enhanced
absorption dosage form as compared to other dosage forms.

25 The term "microparticle", as used herein refers to a drug formulation, in discrete particulate
form, and is interchangeable with the terms "microspheres", ’spherical particles", "microcapsules", "particles", "multiparticulates", "granules", "spheroids", beads" and
"pellets".

30 The term "tablet" as used herein refers to a single dosage form, i.e. the single entity
containing the active pharmaceutical agent that is administered to the subject. The term "tablet" also includes a tablet that may be the combination of one or more "minitablets".

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The term "controlled release matrix" as used herein is defined to mean a dosage form in
which the bupropion hydrobromide or mixtures of bupropion hydrobromide and a second drug, is dispersed within a matrix, which matrix can be either insoluble, soluble, or a combination thereof. Controlled release matrix dosage forms ofthe insoluble type are also
5 referred to as "insoluble polymer matrices", "swellable matrices", or "lipid matrices"
depending on the components that make up the matrix. Controlled release matrix dosage
forms ofthe soluble type are also referred to as "hydrophilic colloid matrices", "erodible matrices", or "reservoir systems". Controlled release matrix dosage forms ofthe invention
refer to dosage forms comprising an insoluble matrix, a soluble matrix or a combination of
10 insoluble and soluble matrices in which the rate ofrelease is slower than that of an uncoated
non-matrix conventional or immediate release dosage forms or uncoated "normal release
matrix" dosage forms. Controlled release matrix dosage forms can be coated with a "control-releasing cost" to further slow the release ofthe bupropion salt from the controlled release matrix dosage form. Such coated controlled release matrix dosage forms can exhibit
15 "modified-release", controlled-release", "sustained-release", "extended-release", "prolonged-
release", "delayed-release" or combinations thereof ofthe active drug.

The term "normal release matrix" as used herein is defined to mean dosage forms in which
the bupropion hydrobromide or mixtures of bupropion hydrobromide and a second drug, is
20 dispersed within a matrix, which matrix can be either insoluble, soluble, or combinations
thereof but constructed such that the release ofthe active drug mimics the release rate of an
uncoated non-matrix conventional or immediate release dosage form comprising the drug.
. The release rate from normal release matrix dosage forms can be slowed down or modified in
conjunction with a controlled release coat.
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The terms "osmotic dosage form", "osmotic delivery device", "modified release osmotic
dosage form" or "controlled release osmotic dosage form" as used herein are used interchangeably in this application, and are defined to mean dosage forms which dispense the
bupropion hydrobromide or mixture ofbupropion hydrobromide and a second drug, all or in
30 part as a result ofthe presence of an osmotic agent in the dosage form driving solvent (e.g.
water, dissolution media, gastric fluid, intestinal fluid, or mixtures thereof) into the core of
the dosage form, which subsequently facilitates the release of drug from the core.

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The terms "osmotic agent", "osrnagcnt", "osmotically effective solute", "osmotic enhancer" "osmotically effective Œompounds","osmotic solutes", "osmopolymer" and "osmotic fluid imbibing agents" as used herein are used interchangeably, and define any material that is
soluble (i.e. can be partially or totally solubilized) or swellable’in a solvent (e.g, water) that enters the composition, and which exhibits an osmotic pressure gradient across the selectively-permeable membrane (e.g. controlled release coat), thus increasing the hydrostatic
pressure inside the osmotic dosage form.

The terms "controlled release coat", "control releasing coat", "modified release coat" and
10 "rate-controlling coat" as used herein are used interchangeably in this application, and are
defined to mean a functional coat which comprises at least one modified release polymer. SNon-limiting examples ofmodified release polymers include pH independent polymers, pH dependent polymers (such as for example enteric or reverse enteric types), soluble polymers,
insoluble polymers, lipids, lipidic materials, and mixtures thereof. When applied onto a
15 dosage form, the controlled release coat can modify (e.g. slow) the rate ofrelease ofthe
active drug. For example, the controlled release coat can be designed such that when the coat
is applied onto a dosage fonn, the dosage form in conjunction with the controlled release
coat, exhibits a "modified-release", "controlled-release", "sustained-release", "extended-
release" and/or "delayed-release" profile. Combinations thereof are permissible. The
20 controlled release coat can optionally comprise additional materials that can alter the
functionality ofthe controlled release coat. The term "modified release" is interchangeable
with the terms "controlled release", "control releasing" and "rate controlling". The term
"coat" is interchangeable with the term "coating"

25 The terms "moisture barrier" and "moisture barrier coat" as used herein are used
interchangeably and are defined to mean a coating which impedes or retards the absôtion of moisture. It is known that bupropion salts are hygroscopic and, as such, are susceptible to decomposition over time under high humidity conditions. Other active drugs can also be susceptible to decomposition over time under high humidity conditions. The proportion ofthe
30 components ofthe moisture barrier and the amount ofthe moisture barrier applied onto the
controlled release coat is such that the moisture barrier does not fall within the USP definition
and requirement for an enteric coat. Suitably, the moisture barrier is comprised of an enteric and/or acrylic polymer, suitably an acrylic polymer, optionally a plasticizer, and a permeation

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enhancer. The permeation enhancer is a hydrophilic substance, which allows water to enter without physical disruption of the coating. The moisture barrier can additionally contain other conventional inert excipients, which can improve processing ofthe extended-release formulation described herein.

The term "enteric coat" as used herein is defined to mean a coating or barrier applied to a
dosage form that can control the location in the digestive system where the active drug(s) is absorbed. For example, an enteric coating can be used to: (i) protect the drug from the destructive action ofthe enzymes or low pH environment ofthe stomach; (ii) prevent nausea
10 or bleeding associated with the irritation ofthe gastric mucosa by the drug; and/or (iii) deliver
the drug in an undiluted form in the intestine. Based on these criteria, in certain
embodiments, the enteric coated dosage form can be regarded as a type of delayed release
dosage form. They differ from sustained release dosage forms in that with sustained release dosage forms, the drug release is extended over a period oftime to maintain therapeutic blood
15 levels and to decrease the incidence ofside effects caused by a rapid release; whereas, with

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enteric coatings, the primary objective is to confine the release ofthe drug to a predetermined region ofthe gastrointestinal tract. Enteric coatings work by presenting’a,surface that is substantially stable at acidic pH, but breaks down at higher pH to allow release ofthe drug in
the intestine.

The term "enteric polymer" as used herein is defined to mean a polymeric substance that
when used in an enteric coat formulation, is substantially insoluble and/or substantially stable under acidic conditions exhibiting a pH ofless than about 5 and which are substantially
soluble or can decompose under conditions exhibiting a pH of about 5 or more. Non-limiting
25 examples ofsuch enteric polymers include carboxymethylethylcellulose, cellulose acetate
phthalate, cellulose acetate succinate, methylcellulose phthalate,
hydroxymethylethylcellulose phthalate, hydroxypropyimethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, polyvinyl alcohol phthalate, polyvinyl
butyrate phthalate, polyvinyl acetal phthalate, a copolymer of vinyl acetate/maleic anhydride,
30 a copolymer ofvinylbutylether/maleic anhydride, a copolymer ofstyrene/maleic acid
monoester, a copolymer ofmethyl acrylate/methacrylic acid, a copolymer ofstyrene/acrylic acid, a copolymer ofmethyl acrylate/methacrylic acid/octyl acrylate, a copolymer of methacrylic acid/methyl methacrylate and mixtures thereof Enteric polymers can be used

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individually or in combination with other hydrophobic or hydrophilic polymers in an enteric coat, a normal release matrix core, a controlled release matrix core, and/or in a controlled release coat. Enteric polymers can be combined with other pharmaceutically acceptable excipients to either facilitate processing of a coat comprising the enteric polymer or to alter
the functionality ofthe coat.

The term "functional coat" as used herein is defined to mean a coating that affects the rate of release in-vitro or in-vivo ofthe active drug(s).

10 The term "non-functional coat" as used herein is defined to mean a coating that does not
substantially affect the rate ofrelease in-vitro or in-vivo ofthe active drug, but can enhance
the chemical, biological, physical stability characteristics, or the physical appearance ofthe modified release dosage form.

15 The term "core" as used herein is defined to mean a solid vehicle in which at least one active
drug is uniformly or non-uniformly dispersed. The core can be formed by methods and
materials well known in the art, such as for example by compressing, fusing, or extruding the active drug together with at least one pharmaceutically acceptable excipient. The core can be manufactured into, for example, a homogenous or non-homogenous unitary core, a
20 mhltiparticle, or a plurality ofmicroparticles compressed into a unitary core. Non-limiting
examples of cores include microparticle cores, matrix cores, and osmotic cores. The core(S)
can be coated with at least one functional coat and/or non-functional coat.

The terms "modified release matrix core", "controlled release matrix core" or "matrix core"
25 when referring to a controlled release matrix dosage form, as used herein are used
interchangeably, and are defined to mean a core in which at least one active drug is dispersed within a matrix which controls or delays the rclease ofthe active drug over a 24-hour period
so as to allow a composition comprising the modified release matrix core to be administered
as a once-a-day composition. The release rate ofthe active drug from the modified release
30 matrix core can be modified by the porosity and tortuosity ofthe matrix, (i.e. its pore
structure). The addition of pore-forming hydrophilic salts, solutes, or wicking agents can influence the release rate, as can the manipulation of processing parameters. For example,
the compression force used in the manufacture ofthe modified release matrix core can alter

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the porosity ofthe matrix core and hence the rate ofrelease ofthe active drug. It will be understood by one of ordinary skill in the art of drug delivery that a more rigid matrix will be less porous and hence release the active drug more slowly compared to a less rigid modified release matrix core. The modified release matrix core can comprise insoluble or inert matrix dosage forms, swellable matrix dosage forms, swellable and erodable matrix dosage form, hydrophobic matrix dosage forms, hydrophilic matrix dosage forms, erodable matrix dosage forms, reservoir dosage forms, or any combination thereof. The modified release matrix core
can comprise at least one insoluble matrix, at least one swellable matrix, at least one
swellable and erodable matrix, at least one hydrophobic matrix, at least one hydrophilic
10 matrix, at least one erodable matrix, or a combination thereofin which the rate ofrelease is
slower than that of uncoated immediate-release dosage forms. Modified release matrix cores
can. be coated with at least one controlled release coat to further slow the release ofthe active drug from the modified release matrix core. Such coated modified release matrix cores can exhibit modified-release, controlled-release, sustained-release, extended-release, prolonged-
15 release, bi-phasic release, delayed-release or combinations thereof ofthe active drug.
Modified release matrix cores can also be coated with a non-functional soluble coat.

The term "plasticizer" as used herein includes any compounds capable of plasticizing or
softening a polymer or a binder used in the present invention. The use of plasticizers is
20 optional, and can be included in the dosage form to modify the properties and characteristics
ofthe polymers used in the coat(s) or core ofthe dosage form for convenient processing
during manufacture ofthe coat(s) and/or the core ofthe dosage form. Once the coat(s)
. and/or core have been manufactured, certain plasticizers can function to increase the
hydrophilicity ofthe coat(s) and/or the core ofthe dosage form in the environment ofuse.
25 During manufacture ofthe coat(s) and/or core, the plasticizer can lower the melting
temperature or glass transition temperature (softening point temperature) ofthe polymer or
binder. Plasticizers can be included with a polymer and lower its glass transition temperature
or softening point. Plasticizers also can reduce the viscosity of a polymer. Plasticizers can
impart some particularly advantageous physical properties to the dosage forms ofthe
30 invention.

The terms "pore former", "pore forming agent", and "pore forming additive" as used herein
are used interchangeably in this application, and are defined to mean an excipient that can be

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added to a coating (e.g. the controlled release coat), wherein upon exposure to fluids in the environment ofuse, the pore former dissolves or leaches from the coating to form pores, channels or paths in the coating, that can fill with the environmental fluid and allow the fluid
to enter the core and dissolve the active drug, and modify the release characteristics ofthe formulation. The pore formers can be inorganic or organic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use.

The term "steady state" as used herein means that the blood plasma concentration curve for a given drug does not substantially fluctuate after repeated doses to dose ofthe formulation.

"AUC" as used herein means area under the plasma concentration-time curve, as calculated
by the trapezoidal rule over a time interval (e.g. complete 24-hour interval); and signifies the extent ofthe absorption of a drug.

15 "Cmax" as used herein means the highest plasma concentration of the drug attained within

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the dosing interval (e.g., 24 hours).

"Cmin" as used herein means the minimum plasma concentration ofthe drug attained within
the dosing interval (e.g. 24 hours).

"Cavg" as used herein means the plasma concentration ofthe drug within the dosing interval (e.g. 24-hours), and is calculated as AUC/dosing interval.

"Tmax" as used herein means the time period, which elapses after administration ofthe
25 dosage form at which the plasma concentration ofthe drug attains the highest plasma
concentration of drug attained within the dosing interval (e.g. 24 hours).

The term "bioequivalence" as used herein is defined as there being about a 90% or greater probability that the bioavailability (AUC) ofthe active drug as determined by standard
30 methods is from about 80% to about 125% ofthe second orally administrable dosage form
comprising the same dose ofthe active drug and that there is about 90% or greater probability that the maximum blood plasma concentration (Cmax) ofthe active drug as measured by
standard methods is from about 80% to about 125% ofthe second orally administrable

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dosage form. For example, the reader is referred to the final version ofthe guidance approved by the US Food and Drug Administration at the time offiling ofthis patent application i.e., the March 2003 Guidance for Industry Bioavailability and Bioequivalence Studies for Orally Administered Drug Products General Considerations, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER, for a detailed discussion on bioequivalence.

The terms "a", "an" or "at least one" as used herein are used interchangeably in this
application, and are defined to mean "one" or "one or more".
10 The numerical parameters set forth in the following specification and attached claims that are
modified by the term "about", are approximations that can vary depending upon the technological properties ofthe particular case. For example, the term "about" can mean
within an acceptable error range (e.g. standard deviations) for the particular value as
determined by one of ordinary skill in the art, which will depend in part on how the value is
15 measured or determined, e.g., the limitations ofthe measurement system.
Other terms are defined as they appear in the following description and should be construed
in the context with which they appear.

The present invention encompasses the bupropion hydrobromide salt and compositions
20 containing safe and pharmaceutically effective levels ofthe bupropion hydrobromide salt,
that can be used for the treatment of a condition in subjects that can benefit from bupropion administration, wherein the bupropion hydrobromide salt and compositions containing safe
and pharmaceutically effective levels ofthe bupropion hydrobromide salt unexpectedly
provide for the reduction ofincidences of and/or the reduction in severity of bupropion-
25 induced seizures, and are more stable, as compared with equivalent molar amounts of
bupropion hydrochloride or otherwise similar or identical compositions containing equivalent molar amounts of bupropion hydrochloride.

Also, the present invention encompasses polyinorphs thereof and specific purified
30 enaritiomeric forms thereof. The present invention also encompasses the use ofsuch
bupropion hydrobromide salt and compositions containing the bupropion hydrobromide salt
for the treatment of one or more conditions in a subject suitable for treatment by bupropion. or pharmaceutically acceptable salts thereof (e.g. depression, obesity, nicotine addiction, and

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other conditions treatable with bupropion such as arc disclosed herein); wherein the incidences of and/or the severity ofbupropion-induced seizures is reduced as compared with an equivalent molar amount of bupropion hydrochloride or an otherwise similar or identical composition containing an equivalent molar amount ofbupropion hydrochloride.

The present invention encompasses any medicament containing a pharmaceutically effective amount of bupropion hydrobromide. This includes both oral and non-orally administrable medicaments such as toicals, injectables, aerosols and other inhalable medicameilts. Particularly such medicament compositions include orally administrable modified release
10 dosage forms containing bupropion hydrobromide. The dosages can be conveniently
presented in unit dosage form and prepared by any ofthe methods well-known in the art of pharmacy. A "solid,dosage form" as used herein, means a dosage form that is neither liquid nor gaseous. Dosage forms include solid dosage forms, such as tablets, powders, microparticles, capsules, suppositories, sachets, troches, patches and lozenges as well as
15 liquid suspensions and elixirs. Capsule dosages contain the solid composition within a
capsule that can be made of gelatin or other conventional encapsulating material.

The modified release dosage forms contemplated in the present invention can be
multiparticulate or monolithic. For example, those skilled in the pharmaceutical art and the
20 design ofmedicaments are aware ofmodified release matrices conventionally used in oral
pharmaceutical compositions adopted for modified release and means for their preparation.

A modified release formulation containing bupropion hydrobromide according to the present invention can be coated with one or more functional or non-functional coatings. Non-
25 limiting examples offunctional coatings include controlled release polymeric coatings,
moisture barrier coatings, enteric polymeric coatings, and the like. In at least one embodiment ofthe present invention a bupropion hydrobromide composition comprises a controlled
release polymeric coating that includes an acrylic polymer. Suitable acrylic polymers include
but are not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate
30 copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aniinoallcyl methacrylate
copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylaniine
copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), polyacrylamide, poly(methacrylic acid anhydride), glycidyl methacrylate copolymers and mixtures thereof.

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In at least one embodiment polynierizable quaternary ammonium compounds are employed
in the controlled release coat, ofwhich non-limiting examples include quaternized
amino aikyl esters and aminoallcyl amides of acrylic acid and methacrylic acid, for example 0-
5 methacryl-oxyethyl-trimethyl-ammonium methos ulfate, f3-acryloxy-propyl-trimethyl-
ammonium chloride, trimethylaminomethyl-methacrylamide methosulfate and mixtures
thereof The quaternary ammonium atom can also be part of a heterocycle, as in methacryloxyethylmethyl-morpholiniom chloride OT the corresponding piperidinium salt, or it
can be joined to an acrylic acid group or a methacrylic acid group by way of a group
10 containing hetero atoms, such as a polyglycol ether group. Further suitable polymerizable
quaternary ammonium compounds include quatemized vinyl-substituted nitrogen

49 heterocycles such as methyl-vinyl pyridinium. salts, vinyl esters of quatemized amino
carboxylic acids, styryltrialkyl ammonium salts, and mixtures thereof. Other polym.erizble
quaternary ammonium compounds useful in the present invention include acryl- and
15 methacryl-oxyethyltrirnethyl-ammoniurn chloride and methosulfate,

20

benzyldimethylammoniumethyl-methacrylate chloride, diethylmethylammoniumethyl-
acrylate and -methacrylate methosulfate, N-trimethylammoniumpropylrnethacrylamide
chloride, N-trimethylanimonium-2,2-dimethylpropyl- 1 -methacrylate chloride and mixtures thereof.

In at least one embodiment the acrylic polymer ofthe controlled release coat is comprised of
one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers (e.g. EUDRAGITfi RS and P1) are described in National Formulary (NF) XVII as fully
polymerized copolymers of acrylic and methacrylic acid esters with a low content of
25 quaternary ammonium groups. Two or more ammonio methacrylate copolymers having
differing physical properties can be incorporated in the controlled release coat of certain embodiments. For example, it is known that by changing the molar ratio ofthe quaternary

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ammonium groups to the neutral(meth)acrylic esters, the permeability properties ofthe resultant coating can be modified.

In certain other embodiments ofthe present invention, the controlled release coat further includes a polymer whose permeability is pH dependent, such as anionic polymers
synthesized from methacrylic acid and methacrylic acid methyl ester (e.g. EUDRAGITfi L

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and EUDRAGITfi S). The ratio of free carboxyl groups to the esters is known to be 1:1 in EUDRAGITfi L and 1:2111 EUDRAGITfi S. EUDRAGITfi L is insoluble in acids and pure water, but becomes increasingly permeable above pH 5.0. EUDRAGITfi S is similar, except that it becomes increasingly permeable above pH 7. The hydrophobic acrylic polymer
5 coatings can also include a polymer which is cationic in character based on
dimethylaminoethyl methacrylate and neutral methacrylic acid esters (e.g. EUDRAGITfi E).
The hydrophobic acrylic polymer coatings of certain embodiments Of the present invention
can further include a neutral copolymer based on poly (meth)acrylates, such as EUDRAGITfi NE. EUDRAGITfi NE 30D lacquer films are insoluble in water and digestive fluids, but
10 permeable and swellable.

In at least one other embodiment ofthe invention, the controlled release coat comprises a dispersion ofpoly (ethylaciylate, methyl methaeryiÆte) 2:1 (KOLLICOATfiEMM 30 D).

15 In at least one othcrernbodiment ofthe invention, the controlled release coat comprises a
polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as KOLLICOATfi SR30D, The dissolution profile can be altered by changing the relative amounts of different acrylic resin lacquers included in the coating. Also, by changing the
molar ratio of polymerizable permeability-enhancing agent (e.g., the quaternary ammonium
20 compounds) to the neutral (meth)acrylic esters, the permeability properties (and thus the
dissolution profile) ofthe resultant coating can be modified.

In at least one embodiment ofthe invention the controlled release coat comprises
ethylcellulose, which can be used as a dry polymer (e.g. ETHOCELfi) solubilised in organic
25 solvent prior to use, or as an aqueous dispersion. One suitable commercially-available
aqueous dispersion of ethylcellulose is AQUACOATfi. AQUACOATfi can be prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the
same in water in the presence of a surfactant and a stabilizer. After homogenization to
generate submicron droplets, the organic solvent can be evaporated under vacuum to form a
30 pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing
phase. Thus, prior to using the same as a coating, the AQUACOATfi can be intimately
mixed with a suitable plasticizer prior to use. Another suitable aqueous dispersion of ethylcellulose is commercially available as SURELEASEfi. This product can be prepared by

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incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of
a polymer, plasticizer (e.g. dibutyl sebacate), and stabilizer (e.g. oleic acid) can be prepared
as a homogeneous mixture, which can then be diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Other examples ofpolymers that can be used in the controlled release coat include cellulose acetate phthalatc, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, shellac; hydro gels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium
10 carmellose, sodium carboxymethyl starch, poly vinyl alcohol, hydroxyethyl cellulose, methyl
cellulose, ethyl cellulose, gelatin, starch, and cellulose based cross-linked polymers in which
the degree of crosslinking is low so as to facilitate adsorption of water and expansion ofthe polymer matrix, hydroxypropyl cellulose, hydroxypropyl methylcellulose,
polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, puliulan,
15 collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic
polymers) poly(hydroxyalkyl methacrylate) (molecular weight from about 5k to about
5000k), polyvinylpyrrolidone (molecular weight from about 10k to about 3601c), anionic and cationic hydrogels, zein, polyamides, polyvinyl alcohol having a low acetate residual, a
swellable mixture of agar and carboxymethyl cellulose, copolymers ofmaleic anhydride and
20 styrene, ethylene, propylene or isobutylene, pectin (molecular weight from about 30k to
about 300k), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, POLYOXfi polyethylene oxides (molecular weight from about 100k to
about 5000k), AQUAKEEPfi acrylate polymers, diesters of polyglucan, crosslinked
polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, hydrophilic polymers such as
25 polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose,
hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro
cellulose, carboxymethyl cellulose, cellulose ethers, methyl ethyl cellulose, ethyihydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, starch, maltodextrin, puliulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol
30 fatty acid esters, polyacrylamide, polyacrylic acid, natural gums, lecithins, pectin, alginates,
ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as arabic, karaya, locust bean, tragacanth, carrageens, guar, xanthan, seleroglucan and mixtures thereof.

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In at least one embodiment the dosage forms are coated with polymers in order to facilitate mucoadhsion within the gastrointestinal tract. Non-limiting examples of polymers that can
be used for mucoadhesion include carboxymethylcellulose, polyacrylic acid, CARBOPOLTM, POLYCARBOPHILTM, gelatin, other natural or synthetic polymers, and mixtures thereof.

In at least one embodiment ofthe invention, the dosage form is an extended release tablet comprising: (i) a core that includes bupropion hydrobromide in an amount offrom about 40%
to about 99% by weight oftablet dry weight, including all values and ranges therebetween, a
10 binder such as polyvinyl alcohol in an amount of from about 05% to about 25% by weight of
tablet thy weight, including all values and ranges therebetween, and a lubricant such as
glyceiyl behenate in an amount of from about 0.1% to about 5% by weight oftablet dry
weight, including all values and ranges therebetween; and (ii) a controlled release coat that includes a water-insoluble water-permeable film-forming polymer such as ethylcellulose in
15 an amount of from about 1% to about 12% by weight oftablet-dry weight, including all
values and ranges therebetween, a water.-soluble polymer such as polyvinylpyrrolidone (POVIDONEfi USP) in an amount of from about 1.5% to about 10% by weight of tablet dry weight, including all values and ranges therebetween, optionally a plasticizer such as dibutyl sebacate, polyethylene glycol 4000 or a mixture thereof, in an amount of from about 0.5% to
20 about 4% by weight oftablet dry weight, including all values and ranges therebetween, and
optionally a wax such as carnauba wax in an amount offrom about 0.01% to about 0.05% by weight oftablet dry weight, including all values and ranges therebetween.

In at least one embodiment ofthe invention, the dosage form is a 174 mg extended release
25 tablet comprising: (i) a core that includes bupropion hydrobromide (e.g. about 81% by weight
oftablet dry weight), a binder such as polyvinyl alcohol (e.g. about 3% by weight oftablet
dry weight), and a lubricant such as glyceryl behenate (e.g. about 3% by weight oftablet dry weight); and (ii) a controlled release coat that includes a water-insoluble water-permeable film-forming polymer such as ethylcellulose (e.g. about 7% by weight oftablet dry weight), a
30 water-soluble polymer such as polyvinylpyrrolidone POV1DONEfi USP), (e.g. about 4% by
weight oftablet dry weight), optionally a plasticizer such as dibutyl sebacate, polyethylene
glycol 4000 or a mixture thereof (e.g. about 2% by weight oftablet dry weight), and
optionally a wax such as carnauba wax (e.g. about 0.03% by weight oftablet dry weight).

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In at least one embodiment ofthe invention, the dosage form is a 348 mg extended release
tablet comprising: (i) a core that includes bupropion hydrobromide (e.g. about 87% by weight oftablet dry weight), a binder such as polyvinyl alcohol (e.g. about 3% by weight oftablet
5 dry weight), and a lubricant such as glyceryl behenate (e.g. about 3% by weight oftablet dry
weight); and (ii) a controlled release coat that includes a water-insoluble water-permeable film-forming polymer such as ethylcellulose (e.g. about 4% by weight oftablet dry weight), a water-soluble polymer such as polyvinylpyrrolidone (POVIDONEfi USP), (e.g. about 2% by weight oftablet dry weight), optionally a plasticizer such as dibutyl sebacate, polyethylene
10 glycol 4000 or a mixture thereof(e.g. about 1% by weight oftablet dry weight), and
optionally a wax such as carnauba wax (e.g. about 0.01% by weight oftablet dry weight).

In at least one embodiment ofthe invention, the dosage form is a 522 mg XL tablet
comprising: (i) a core that includes bupropion hydrobromide (e.g. about 85% by weight of
15 tablet dry weight), a binder such as polyvinyl alcohol (e.g. about 3.5% by weight oftablet dry
weight), and a lubricant such as glyceryl bchcnate (e.g. about 3.5% by weight oftablet dry weight); and (ii) a controlled release coat that includes a water-insoluble water-permeable film-forrning polymer such as ethylcellulose (e.g. about 3% by weight oftablet dry weight), a water-soluble polymer such as polyvinyipyrrolidone (POVIDONEfi USP), (e.g. about 3.5%
20 by weight of tablet dry weight), optionally a plasticizer such as dibutyl sebacate, polyethylene
glycol 4000 or a mixture thereof (e.g. about 1.5% by weight oftablet dry weight), and
optionally a wax such as carnauba wax (e.g. about 0.01% by weight oftablet dry weight).

In addition to the modified release dosage forms described herein, other modified release
25 technologies known to those skilled in the art can. be used in order to achieve the modified
release formulations of certain embodiments ofthe present invention. Such formulations can
be manufactured as a modified release oral formulation, for example, in, a suitable tablet or multiparticulate formulation known to those skilled in the art. In either case, the modified release dosage form can optionally include a controlled release carrier which is incorporated
30 into a matrix along with the drug, or which is applied as a controlled release coating.

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Tablets

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In certain embodiments ofthe present invention, there is provided a modified-release tablet having a core comprising bupropion hydrobromide and conventional excipients, wherein the bupropion hydrobromide salt or the composition comprising the bupropion hydrobromide
5 provides for the reduction ofincidences of and/or severity ofbupropion-induced seizures, and
is more stable as compared with equivalent molar amounts of bupropion hydrochloride or otherwise similar or identical compositions containing equivalent molar amounts of
bupropion hydrochloride. The core can be surrounded by a controlled release coat which can control the release of bupropion hydrobromide or mixture of bupropion hydrobromide with a
10 second drug. In other embodiments, a moisture barrier can optionally be added to surround
the controlled release coat. This moisture barrier is optional given the enhanced stability of bupropion hydrobromide relative to bupropion hydrochloride and by selection of an
appropriate controlled release coating. Ifpresent, this moisture barrier can affect in-vitro
drug release as well as precluding moisture from coming into contact with the bupropion
15 hydrobromide salt. Optionally, this tablet can further comprise one or more additional
functional or non-functional coatings surrounding the core, moisture barrier and/or controlled release coat.

Extended Release (L) Tablets
20 In certain embodiments ofthe present invention, there is provided an extended-release (XL)
tablet having a core comprising bupropion hydrobromide and conventional excipients,
wherein the bupropion hydrobromide salt provides for the reduction ofincidences of and/or severity of bupropion-induced seizures, and is more stable, as compared with equivalent
molar amounts of bupropion hydrochloride. The core can be surrounded by a controlled
25 release coat, which controls the release ofthe bupropion hydrobromide salt. The tablet
optionally can comprise one or more additional functional or non-functional coats
surrounding the core or controlled release coat. The extended-release tablet of certain embodiments has unexpected enhanced stability.

30 The XL Core
The core of the extended-release tablet comprises an effective amount ofthe bupropion hydrobromide salt, a binder, and a lubricant; and can contain other conventional inert
excipients. The amount ofthe bupropion hydrobromide salt present in the XL core can vary

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in an amount from about 40% to about 99% by weight ofthe tablet dry weight, including all values and ranges therebetween. For example, in certain embodiments bupropion hydrobromide is present in an amount from about 70% to about 95% by weight ofthe tablet
dry weight, including all values and ranges therebetween. For example, in certain
embodiments, the core comprises bupropion hydrobromide in a proportion of about 40%,
about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about
80%, about 85%, about 90%, about 95% or about 99% ofthe core dry weight.

In at least one embodiment of a 174mg dose tablet, the bupropion hydrobromide is present in
10 an amount of from about 75% to about 85% by weight ofthe tablet dry weight, including all
values and ranges therebetween. In at least one embodiment of a 348 mg dose tablet, the
amount of bupropion hydrobromide can be present in an amount offrom about 80% to about 90% by weight of the tablet dry weight, including all values and ranges therebetween. In at
least one embodiment of a 522mg dose tablet, the bupropion hydrobromide is present in an
15 amount of from about 75% to about 90% by weight ofthe tablet dry weight, including all
values and ranges therebetween. In certain embodiments ofthe 174mg, 348mg and 522mg
dose bupropion hydrobromide extended-release tablets ofthe invention, the amount of
bupropion hydrobromide is present in an amount of from about 85% to about 99% by weight
ofthe dry core for each dose, including all values and ranges therebetween.
20

A binder (also sometimes called adhesive) can be added to a drug-filler mixture to increase
the mechanical strength ofthe granules and tablets during formation. Binders can be added
. to the formulation in different ways: (1) as a dry powder, which is mixed with other
ingredients before wet agglomeration, (2) as a solution, which is used as agglomeration liquid
25 during wet agglomeration, and is referred to as a solution binder, and (3) as a dry powder,
which is mixed with the other ingredients before compaction. In this form the binder is
referred to as a dry binder. Solution binders are a common way ofincorporating a binder into granules. In certain embodiments, the binder used in the XL tablets is in the form of a
solution binder. Non-limiting examples of binders useful for the core include hydrogenated
30 vegetable oil, castor oil, paraffin, higher aliphatic alcohols, higher aliphatic acids, long chain
fatty acids, fatty acid esters, wax-like materials such as fatty alcohols, fatty acid esters, fatty
acid glycerides, hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol, hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures thereof.

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Specific examples ofwater-soluble polymer binders include modified starch, gelatin, polyvinylpyrrolidoue, cellulose derivatives (such as for example hydroxypropyl.
methylcellulose (HPMC) and hydroxypropyl cellulose (HPC)), polyvinyl alcohol and
mixtures thereof. The amount of binder present can vary from about 0.5% to about 25% by
5 weight ofthe tablet dry weight, including all values and ranges therebetween. For example,
in certain embodiments the binder is present in an amount of from about 0.5% to about 15%
by weight ofthe tablet dry weight, including all values and ranges therebetween For
example, in certain embodiments ofthe 174mg, 348mg and 522mg dose tablets, the binder is present in an amount of from about 1% to about 6% by weight of each dry core weight,
10 including all values and ranges therebetween; and in other embodiments at about 3% by
weight of each dry core weight. In at least one embodiment ofthe 522mg dose tablet, the binder is present in an amount of about 4% by weight of dry core weight. In at least one embodiment ofthe invention the binder is polyvinyl alcohol.

15 Lubricants can be added to pharmaceutical formulations to decrease any friction that occurs
between the solid and the die wall during tablet manufacturing. High friction during
tabletting can cause a series of problems, including inadequate tablet quality (capping or even fragmentation oftablets during ejection, and vertical scratches on tablet edges) and may even
stop production. Accordingly, lubricants are added to tablet formulations of certain
20 embodiments ofthe XL tablet formulation described herein. Non-limiting examples of
lubricants useful for the core include glyceryl beheriate, stearic acid, hydrogenated vegetable
oils (such as hydrogenated cottonseed oil (STERPTEXfi), hydrogenated soybean oil (STEROTEX fi 1-IM) and hydrogenated soybean oil & castor wax (STERPTEXfi K), stearyl alcohol, leucine, polyethylene glycol (MW 1450, suitably 4000, and higher), magnesium
25 stearate, glyceryl monostearate, stearic acid, polyethylene glycol, ethylene oxide polymers
(e.g. CARBOWAXfi), sodium lauryl sulfate, magnesium laurylsulfate, sodium oleate,
sodium stearyl furnarate, DL-leucine, colloidal silica, mixtures thereof and others as known
in the art. in at least one embodiment ofthe present invention,, the lubricant is glyceryl
behenate (e.g. COMPRITOLfi 888). The amount oflubricant present can vary from about
30 0.1% to about 6% by weight ofthe tablet dry weight, including all values and ranges
therebetween. For example, in certain embodiments the amount of lubricant present is from about 2% to about 3% by weight ofthe tablet dry weight, including all values and ranges therebetween; and in other embodiments the amount of lubricant present is at about 3% by

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weight ofthe tablet dry weight. In certain embodiments ofthe 174mg, 348mg and 522mg
dose XL tablets of the invention, the lubricant is present in an amount of about 3% by weight ofthe tablet dry weight, or from about 1% to about 6% by weight ofthe dry core weight, including all values and ranges therebetween. For example, in certain embodiments the
5 lubricant is present in an amount of about 3% by weight ofthe dry core weight for the
174mg, 348mg and 522mg dose XL tablets. In at least one embodiment ofthe 522mg dose
tablet, the lubricant is present in an amount of about 4% by weight of dry core weight.

At this stage, the XL core formulation of certain embodiments ofthe present invention is an
10 uncoated immediate release formulation resulting in about 100% dissolution ofthe bupropion
hydrobromide salt within about 1 hour. In at least one embodiment the XL core is a normal release matrix formulation. In certain embodiments the core comprises an effective pharmaceutical amount of bupropion hydrobromide, a binder (e.g. polyvinyl alcohol), and a lubricant (e.g. glyceryl behenate). Additional inert excipients consistent with the objects of
15 the invention can also be added to the core formulation. The additional inert excipients can
be added to facilitate the preparation and/or improve patient acceptability ofthe final
extended-release dosage form as described herein. The additional inert excipients are well
known to the skilled artisan and can be found in the relevant literature, for example in the
Handbook of Pharmaceutical Excipients. Non-limiting examples ofsuch excipients include
20 spray dried lactose, sorbitol, mannitol, and any cellulose derivative.

In certain embodiments the core ofthe bupropion hydrobromide composition (e.g. core of an
. XL tablet) can be made according to any one ofthe methods described in US Patent No.
7,241,805.
25

In at least one embodiment ofthe invention, the granules to be compressed to form the core
ofthe bupropion hydrobromide XL tablet ofthe invention described herein, are manufactured
by the wet granulation process. Wet granulation involves agitation of a powder (the active
drug) by convention in the presence of a liquid (the solution binder) followed by drying. For
30 forming the granules, which are to be eventually compressed into the tablet cores, the
bupropion hydrobromide salt is first granulated, for example, with a solution binder, in a granulator, for example using a fluidized bed granulator (e.g. a fluidized. bed granulator manufactured by Glatt (Germany) or Aeromatic (Switzerland)). The binder (e.g. polyvinyl

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alcohol) is first dissolved or dispersed in a suitable solvent (e.g. water). The solution binder is then top sprayed onto the drug in a granulator (e.g. a fluidized bed granulator). Alternatively, granulation can also be performed in a conventional or high shear mixer. If necessary, the additional inert excipients (e.g. a filler) can be mixed with the bupropion hydrobromide salt prior to the granulation step.

The granules formed are subsequently dried and then sieved prior to blending the granules
with the lubricant. In certain embodiments, the dried granules are sieved through a 1.4mm
mesh screen. The sieved granules are then blended with the lubricant, and ifnecessary, any
10 other additional inert excipients, which can improve processing ofthe extended-release
tablets ofthe invention. Blending ofthe granules with the lubricant, and if necessary, any
10 additional inert excipients, such as for example a glidant, can be performed in a V-blender or
any other suitable blending apparatus. Glidants can improve the flowability ofthe powder.
This for example, can be helpful during tablet production at high production speeds and
15 during direct compaction. However, because the requirement for adequate flow is high, a
glidant is often also added to a granulation before tabletting. The blended granules are
subsequently pressed into tablets and are hereinafter referred to as tablet cores. Tablet cores
can be obtained by the use ofstandard techniques and equipment well known to the skilled artisan. For example, the XL tablet cores can be obtained by a rotary press (also referred to
20 as a multi-station press) fitted with suitable punches.

The granules can also be manufactured by using other processes known to the skilled artisan. Examples of other granule manufacturing processes include dry granulation (e.g. slugging,
roller compaction), direct compression, extrusion, spheronization, melt granulation, and
25 rotary granulation.

An example ofthe granulation process for the XL cores (60kg batch) is as follows: A Fluid
Bed Processor is used for granulation in order to agglomerate the particles ofthe materials to obtain a uniform particle size for the final blend. The granulating solution is prepared by
30 dissolving the binder (e.g. polyvinyl alcohol) in hot purified water while mixing. The percent
solids content can be adjusted to obtain a viscosity to control the build up (agglomeration
size) ofthe material. A lower viscosity leads to smaller particles, and a higher viscosity leads
to larger particles. In addition, the application rate (e.g, from about 150 gnilittin to about 250

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gm/mu, including all values and ranges therebetween; or about 200 gm/min), position of Spray gun (e.g. center position) and nozzle size (e.g. from about 0.5 mm to about 2mm4 including all values and ranges therebetween; or about 1mm) and atomization pressure (e.g. from 20 psi to about 40 psi, including all values and ranges therebetween; or about 30 psi) contribute further to control particle size. The active material is fluidized and heated (e.g.
from about 35°C to about 45°C, including all values and ranges therebetween; or about 40°C) prior to start ofsolution application. During the spray cycle, the bed temperature (e.g. from about 35°C to about including all values and ranges therebetween, or about 40°C) is
kept at a constant temperature to avoid over-wetting. Once all the required binder solution is
10 applied, the material is further dried to the targeted LOD value (i.e. loss on drying) (e.g.
below about 1%) prior to unloading. The amount of binder (e.g. polyvinyl alcohol) is from about 2% to about 6%, including all values and ranges therebetween, e.g. about 3%; and the solution concentration is from. about 3% to about 7%, including all values and ranges therebetween, e.g. about 4.5 %. The time of agglomeration process for the 60 kg batch is
15 from about 45 minutes to about 220 minutes including all values and ranges therebetween
e.g. about 150 minutes. Once the granulate is dry, material is passed through a 1,4 and 2.00
mm screen to remove any oversized particles. The oversized particles are passed through the mill to reduce oversize particles. Oversized particles are generally not present man amount
to exceed about 5% oftotal yield. The screened and milled materials are placed into a shell
20 blender (e.g. V-Blender, Bin blender) and the lubricant (e.g. glyceryl behenate) is added. The
lubricant is screened and added to the granules and blended at the predetermined number of revolutions or time (e.g. mix time of about 5 min to about 15 min, including all values and
ranges therebetween; e.g. including about 10 min), The percent lubricant is from about 0.5%
to about 4%, including all values and ranges therebetween (e.g. including about 2%). The
25 level oflubrication is established for sufficient coverage of either larger or smaller particle
size distribution. Additional characteristics include bulk density (e.g.from about 0.3 gm/ml to about 0.8 gm/ml, including all values and ranges therebetween, e.g.includung about 0.5
gm/ml), and moisture content (e.g. not more than about 1%). Particle size and flow of final blend are factors in obtaining uniform fill of cavities on a rotary press. The flow and top
30 rotation speed ofthe press are adjusted (dependant on the type/size of press) so as to not
jeopardize the weight uniformity of individual tablets. The product blend is passed through a hopper into a feed frame to fill the die cavities passing under the feed frame. Weight
adjustments are made to keep the weight within the specified range, and adjustments made to

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the pressure settings to obtain the required hardness. Some components monitored for the tablets are tablet thickness and friability (e.g. less than about 0.5%). Suitable thickness
(related to overall surface area) and lower friability help reduce core damage and loss of
active during coating. Tablet samples are removed at predetermined intervals to monitor
5 specifications.

Coatings
The tablet cores can be coated for administration to a subject. In at least one embodiment of the invention, the tablet cores are coated with a controlled release coating ("XL Controlled
10 Release Coat") that can provide an extended release ofthe bupropion hydrobromide salt or
mixture ofthe bupropion hydrobromide salt and other drug. In at least one other
embodiment, the tablet cores are coated with an aqueous controlled release coating that

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comprises an aqueous dispersion of a neutral ester copolymer without any functional groups ("AQ Controlled Release Coat")

In certain embodiments the tablet dosage form comprises an optional moisture barrier in
addition to the controlled release coat. The controlled release coat and the moisture barrier
can be applied in two stages. The controlled release coat can be applied directly onto the
surface ofthe tablet cores and functions to control the release ofthe.bupropion hydrobromide
20 salt. The moisture barrier can be applied directly onto the surface ofthe controlled release
coat to impede or retard the absorption of moisture.

10 Prophetic examples of controlled release coat formulations are provided below. It should be
understood that the constituents and/or proportions ofthe constituents in these coatings as
25 well as the amounts thereof can be varied in order to achieve formulations possessing

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different release characteristics. In all instances wherein prophetic examples are provided
these compositions are intended to be exemplary and it should be understood that the specific procedures, constituents, amounts thereof and the like can be varied in order to obtain a composition possessing desired properties.

In at least one embodiment the controlled release coat is a coating formulation that provides a delayed release ofthe active drug(s) from the tablet core. In such embodiments the coating formulation to be applied to the core can comprise:

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EUDRAGITfi L12.5
Triethyl citrate
Talc
Isopropyl alcohol
5 Solids total=

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about 50% by weight of coating suspension about 0.63% by weight of coating suspension about 1.25% by weight of coating suspension about 48.12% by weight of coating suspension about 8.1%

Polymer content of suspension = about 6.3%

In certain embodiments the controlled release coating ofthe bupropion hydrobromide dosage form (e.g. controlled release coat of an XL tablet) can be made according to any one ofthe
10 methods described herein.

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Preparation ofthe controlled release coating formulation ofsuch embodiments (e.g.
controlled release coat that can provide a delayed release ofthe active drug) can be as
follows: Talc and triethyl citrate are homogenized in the solvent by means of a homogenizer
for approximately 10 minutes. The suspension is poured directly into the EUDRAGITfi
L12.5 dispersion and stirred gently to avoid sedimentation. The coating is sprayed onto
tablets until approximately 5mg/cm2 of EUDRAGITfi L has been applied to the tablet core.

In at least one embodiment the controlled release coat can provide a sustained release ofthe active drug from the tablet core. The coating formulation can comprise:
EUDRAGITfi RL 12.5 about 10% by weight of coating suspension
EUDRAGITfi RS 12.5
Dibutyl sebacate
Talc
Magnesium stearate
Acetone

Isopropyl alcohol
Solids total

about 30% by weight of coating suspension about 0.5% by weight of coating suspension about 3.5g by weight of coating suspension about 1% by weight of coating suspension about 27.5% by weight of coating suspension about 27.5% by weight of coating suspension about 10%

Polymer content ofsuspension = about 5%

Preparation ofthe controlled release coating formulation of such embodiments (i.e. controlled release coat that can provide a sustained release of the active drug) can be as follows: Dibutyl sebacate, talc and magnesium stearate are mixed and finely dispersed together with the

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diluents acetone and isopropyl alcohol. The suspension is then combined with the EUDRAGITfi polymer dispersions. The coating is sprayed onto the core until approximately
1 Omg/cm2 of polymer has been applied to the core.

5 In at least one embodiment the controlled release coat is a polymer blend coating possessing
pH dependent polymer (e.g. EUDRAGITfi L30D55) in combination with a sustained release polymer (e.g. AQUACOATfi). Such a coating formulation can comprise:
AQUACOATfi (ethylcellulose 30%) about 21% by weight of coating suspension
EUDRAGITfi L30 D 55 about 21% by weight of coating suspensioti
10 Triethyl citrate about 3% by weight of coating suspension
Water about 55% by weight of coating suspension
Solids total = about 15.6%
Polymer content ofsuspension about 12.6%

15 Application ofthe polymer blend coating can be as follows: Coating applied to a 10mg/cm2
application ofpolymer to the drug core.

In at least one embodiment the controlled release coat is a drug coating containing at least
one other drug (e.g. Citalopram) on top of a core containing bupropion hydrobromide salt.
20 The coating formulation can comprise:
KOLLIDONfi VA64 about 2,5% by weight of drug coating suspension
(Vinylpyn’olidone-.vinyl acetate copolymer)
KLUCELTMEF about 2.5% by weight of drug coating suspension
(Hydroxypropylcellulose)
25 Citalopram about 2% by weight of drug coating suspension
Talc about 3% by weight of drug coating suspension
2-propanol about 90% by weight of drug coating suspension
Solids total = about 10%
Polymer content ofsuspension = about 5%
30

Application ofthe drug coating formulation can be as follows: Drug coating is sprayed onto tablets until the desired amount of other drug (e.g. Citaloprarn) is applied.

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A top-coat can subsequently be applied as a cosmetic coating and also to prevent tablet sticking.
The top-coat formulation applied to the drug coated core can comprise:
KOLLIDONfi VA64 about 2.5% by weight oftop-coat suspension
(Vinylpyrrolidone-vinyl acetate copolymer)
KLUCELTM EF about 2.5% by weight oftop-coat suspension
(Hydroxypropylcellulose)
Talc about 2.5% by weight oftop-coat suspension
Isopropyl alcohol about 92.5% by weight oftop-coat suspension
10 Solids total = about 7.5%

Polymer content ofsuspension about 5%

15

Application ofthe top-coating formulation can be as follows: Coating is applied to about a
2% weight gain (expressed as % of drug coated tablet core)

The Extended Release (XL) Controlled Release Coat
The XL controlled release coat is a semi-permeable coat comprising a water-insoluble, water-permeable film-forming polymer, a water-soluble polymer, and optionally a plasticizer.

20 Non-uniting examples of water-insoluble, water-permeable film-forming polymers useful for
the XL controlled release coat of certain embodiments include cellulose ethers, cellulose
esters, polyvinyl alcohol and mixtures thereof. In certain embodiments the water-insoluble, water-permeable film forming polymers can be the ethyl celluloses, and can be selected from
the following non-limiting examples: ethyl cellulose grades PR100, PR45, PR20, PR1O and
25 PR7 (ETHOCELfi, Dow), and any combination thereof. In at least one embodiment ofthe
invention, ethyl cellulose grade PR 100 is the water-insoluble, water-permeable film-forming polymer. In certain embodiments the amount ofthe water-insoluble water-permeable film-forming polymer can vary from about 1% to about 12% by weight ofthe tablet dry weight, including all values and ranges therebeLween. For example, in certain embodiments the
30 amount ofthe water-insoluble water-permeable film-forming polymer is present in an amount
from about 5% to about 10%, and in other embodiments from about 6% to about 8% by
weight ofthe tablet dry weight. In certain embodiments ofthe 174mg dose modified-release tablets ofthe invention, the amount ofwater-insoluble water permeable film-forming

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polymer is from about 3% to about 8% by weight ofthe tablet dry weight, preferably from about 6% to about 7% ofthe tablet dry weight, including all values and ranges therebetween. With respect to the controlled release coat itself, the amount of water-insoluble water-permeable film-forming polymer in certain embodiments ofthe 174mg dose tablet can be
5 from about 35% to about 60% by weight ofthe controlled release coat thy weight, including
all values and ranges therebetween.- and in certain embodiments from about 40% to about
50% by weight ofthe controlled release coat dry weight. In certain embodiments ofthe
348mg dose modified-release tablet ofthe invention, the amount of water-insoluble water-permeable fihn-forming polymer can be from about 2% to about 5% by weight ofthe tablet
10 dry weight, including all values and ranges therebetween, and in other embodiments from
about 3% to about 4% by weight ofthe tablet dry weight. With respect to the controlled
release coat itself, the water-insoluble water-permeable film-forming polymer in certain embodiments ofthe 348mg dose tablet is present in an amount of about 40% by weight ofthe controlled release coat dry weight. In certain embodiments ofthe 522mg dose modified-
15 release tablet ofthe invention, the amount of water-insoluble water-permeable film-forming
polymer can be from about 0.5 to about 10% by weight ofthe tablet dry weight, including
all values and ranges therebetween, and in other embodiments from about 1% to about 6% by weight ofthe tablet dry weight. With respect to the controlled release coat itself, the water-insoluble water-permeable film-forming polymer in certain embodiments ofthe 522mg dose
20 tablet is present in an amount of about 37% by weight ofthe controlled release coat dry
weight.

Non examples ofwater-soluble polymers useful for the XL controlled release coat include polyvi.nylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose and
25 mixtures thereof. In at least one embodiment the water-soluble polymer is
polyvinylpynolidone (POVIDONEfi USP). The amount of water-soluble polymer can vary from about 1.5% to about 10% by weight ofthe tablet dry weight, including all values and ranges therebetween. For example, in certain embodiments the amount ofwater-soluble polymer is from about 3% to about 8%, and in other embodiments at about 4% by weight of
30 the tablet dry weight. With respect to the controlled release coat itself, in certain
embodiments the amount ofwater-soluble polymer present is from about 25% to about 55%
by weight ofthe controlled release coat dry weight, including all values and ranges therebetween. For certain embodiments ofthe 174mg dose ofthe extended release tablet of

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the invention, the amount ofwater-soluble polymer is from about 3% to about 5% by weight ofthe tablet dry weight, including all values and ranges therebetween and from about 25% to about 50% by weight ofthe controlled release coat dry weight, including all values and ranges therebetween. For certain embodiments ofthe 348mg dose ofthe extended release
tablet ofthe invention, the amount of water-soluble polymer present is from about 2% to
about 5% ofthe tablet dry weight including all values and ranges therebetween; and from
about 40% to about 50% by weight ofthe controlled release coat dry weight, including all
values and ranges therebetween. For certain embodiments ofthe 522mg dose ofthe extended release tablet ofthe invention, the amount of water-soluble polymer present is from about 2%
10 to about 5% ofthe tablet dry weight, including all values and ranges therebetween; and from
about 40% to about 50% by weight ofthe controlled release coat dry weight, including all
values and ranges therebetween.

In certain embodiments, the XL controlled release coat further comprises a plasticizer. The
15 use ofplasticizers is optional, and they can be added to film coating formulations to modify
the physical properties of a polymer to make it more usable during manufacturing.
Plasticizers can be high boiling point organic solvents used to impart flexibility to otherwise
hard or brittle polymeric materials. Plasticizers generally cause a reduction in the cohesive intermolecular forces along the polymer chains resulting in various changes in polymer
20 properties including a reduction in tensile strength, and increase in elongation and a reduction
in the glass transition or softening temperature ofthe polymer. The amount and choice ofthe plasticizer can affect the hardness of a tablet and can even affect its dissolution or
disintegration characteristics, as well as its physical and chemical stability. Certain
plasticizers can increase the elasticity and/or pliability of a coat, thereby decreasing the coat’s
25 brittleness. Once the dosage form is manufactured, certain plasticizers can function to
increase the hydrophilicity ofthe coat(s) and/or the core ofthe dosage form in the
environment ofuse (in-vitro or in-vivo). Non-limiting examples ofplasticizers that can be
used in the controlled release coat described herein include acetylated monoglycerides; acetyltributyl. citrate, butyl phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate;
30 dimethyl phthalate; ethyl phthalyl ethyl glycolate; glycerin; propylene glycol; triacetin;
tripropioin; diacetin; dibutyl phthalate; acetyl monoglyceride; acetyltiiethyl citrate,
polyethylene glycols; castor oil; rape seed oil, olive oil, sesame oil, triethyl citrate; polyhydric alcohols, glycerol, glycerin sorbitol, acetate esters, gylcerol triacetate, acetyl triethyl citrate,

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dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidized tallate, triisoctyl trimellitate, diethythexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylliexyl
sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate,
diethylfurnerate, dibutylsuccinate, diethylmalonate, dibutylphthalate, dibutylsebacate,
glyceroltributyrate, polyols (e.g. polyethylene glycol) of various molecular weights, and
mixtures thereof. it is contemplated and within the scope ofthe invention, that a combination ofplasticizers can be used in the present formulation. In at least one embodiment ofthe
10 invention, the plastizer is polyethylene glycol 4000, dibutyl sebacate or a mixture thereof.
The amount of plasticizer for the controlled release coat can vary in an amount of from about

S 0.5% to about 4% by weight ofthe tablet dry weight, including all values and ranges
therebetween. For example, in certain embodiments the plasticizer is present in an amount of
from about 2% to about 3% by weight ofthe tablet dry weight. For certain embodiments of
15 the 174 mg dose extended-release tablet ofthe invention, the amount of plasticizer present in
the controlled release coat is from about 1% to about 4% by weight ofthe tablet dry weight,
including all values and ranges therebetween. For certain embodiments of the 348mg dose
extended release tablet ofthe invention, the amount of plasticizer present is from about 0.5%
to about 4% by weight ofthe tablet dry weight, including all values and ranges therebetween.
20 For certain embodiments ofthe 522mg dose extended release tablet ofthe invention, the
amount of plasticizer present is from about 0.5% to about 4% by weight ofthe tablet dry
weight, including all values and ranges therebetween. In certain embodiments ofthe 174 mg,
40 348 mg and 522 mg dosage forms, the plasticizer is present in an amount offrom about 6% to
about 30% by weight ofthe controlled release coat dry weight, including all values and
25 ranges therebetween. For example, in certain embodiments the plasticizer is present in an
amount of about 12% by weight ofthe controlled release coat dry weight.

The ratio ofwater-insoluble water-permeable film forming polymer:plasticizer:water-soluble
polymer for the XL controlled release coat of certain embodiments ofthe invention described
30 herein can vary from about 3:1:4 to about 5:1:2, including all values and ranges
therebetween. For example, in certain embodiments the ratio ofwater-insoluble water-permeable film forming polymer:plasticizer:watcr-soluble polymer for the XL controlled
release coat is about 4:1:3. For certain other embodiments ofthe XL tablet the ratio ofthe

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water-insoluble water-permeable film-forming polymer:plasticizer:water-soluble polymer in
the XL controlled release coat is from. about 7:2:6 to about 19:5:18, including all values and ranges therebetween. In at least one embodiment the ratio ofwater-insoluble water-
permeable film forming polymer:plasticizer:water-soluble polymer for the XL controlled
5 release coat is about 13:4:12. In at least one embodiment ofthe 522mg dosage form, the ratio
ofwater-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer
for the XL controlled release coat is about 13:6:16.

In certain embodiments the XL controlled release coat ofthe bupropion hydrobrornide tablet
10 can be made according to any one ofthe methods described herein.

Preparation and application ofthe XL controlled release coat can be as follows. The water-insoluble water-permeable film-forming polymer (e.g. ethyl cellulose), and the plasticizer
(e.g. polyethylene glycol 4000), are dissolved in an organic solvent (e.g. a mixture of ethyl
15 alcohol). In the manufacture of embodiments that do not require a plasticizer, the water-
insoluble water-permeable film-forming polymer can be dissolved in the organic solvent
without the plasticizer. The water-soluble polymer (e.g. polyvinyl pyrrolidone) is next added until a homogenous mixture is achieved. The resulting controlled release coat solution is
then sprayed onto the tablet cores using a tablet coater, fluidized bed apparatus or any other
20 suitable coating apparatus known in the art until the desired weight gain is achieved. The
tablet cores coated with the controlled release coat are subsequently dried. In the
manufacture of embodiments that have a moisture barrier, the controlled release coat is dried before the moisture barrier is applied.

25 An example ofthe coating process for the XL controlled release coat is as follows: The XL
controlled release coat solution is prepared by dissolving the water insoluble polymer (e.g, ethylcellulose) and water soluble polymer (e.g. polyvinylpyrrolidone) and an ethyl alcohol mixture while mixing and is followed with the addition ofthe plasticizer(s) (e.g. mixture of polyethylene glycol 4000 and dibutyl sebacate). Once completely dissolved, the solution is
30 homogenized to obtain a uniform mixture of appropriate viscosity. This procedure helps
obtain a complex mix of a water permeable film to control the release ofthe active drug. The composition ofthe solution can be formulated to contain various levels ofthe water insoluble polymer and water soluble polymer and a mix ofthe plasticizer(s). The release function is

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further controlled by the film thickness applied and measured as weight gain ofsolids in the coating required. Tablets are coated in a perforated coating pan with control of pan speed
(e.g. from about 8 rpm to about 14 rpm, including all values and ranges therebetween; and in some cases about 12 rpm), spray rate (e.g. from about 150 gm/min to about 250 gm/mm,
5 including all values and ranges therebetween; and in some cases about 200 gm/mm),
atomization pressure (e.g. from about 15 psi to about 25 psi, including all values and ranges therebetween; and in some cases about 20 psi), supply volume (from about 800 to about 1000
cubic ft/mm, including all values and ranges therebetween, and in some cases about 900
cubic ft/mm), and air temperature (e.g. from about 50°C to about 60°C, including all values
10 and ranges therebetween; and in some cases about 55°C), monitored through a bed
temperature and/or outlet temperature of from about 38°C to about 42°C, including all values Sandranges therebetween;and in some cases about 40°C. On completion ofthe coating cycle, tablets are dried and unloaded into bulk containers. The printing process comprises the
transfer of a print image from a print plate covered with edible black ink and transferred via a
15 print roll or print pad onto the surface ofthe tablets. The printed tablets are transferred
through a drying element prior to discharging into bulk containers. Samples for final testing
are taken throughout the printing process.

The skilled artisan will appreciate that controlling the permeability can control the release of
20 the bupropion hydrobromide salt and/or the amount of coating applied to the tablet cores.
The permeability ofthe XL controlled release coat can be altered by varying the ratio ofthe water-insoluble, water-permeable film-forming polymer:plasticizcr:water-soluble polymer

5 and/or the quantity of coating applied to the tablet core. A more extended release can be
obtained with a higher amount ofwater-insoluble, water-permeable film forming polymer.
25 The addition of other excipients to the tablet core can also alter the permeability ofthe
controlled release coat. For example, ifit is desired that the tablet core further comprise an
expanding agent, the amount of plasticizer in the controlled release coat could be increased to
make the coat more pliable, as the pressure exerted on a less pliable coat by the expanding
agent could rupture the coat. Further, the proportion ofthe water-insoluble water-permeable
30 film forming polymer and water-soluble polymer can also be altered depending on whether a
faster or slower dissolution and/or release profile is desired.

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Depending on the dissolution or in-vivo release profile desired, the weight gained after
coating the tablet core with the XL controlled release coat typically can vary from about 3%
to about 30% ofthe weight ofthe dry tablet core, including all values and ranges therebetween. For a 174 mg dose extended release tablet according to certain embodiments,
5 the weight gain can typically vary from about 10% to about 17% ofthe weight ofthe dry
tablet core, including all values and ranges therebetween, For the 348 mg dose extended release tablet of certain embodiments, the weight gain can vary from about 7% to about 10% ofthe weight ofthe dry tablet core, including all values and ranges therebetween For the
522 mg dose extended release tablet of certain embodiments, the weight gain can vary from
10 about 5% to about 15% ofthe weight of the dry tablet core, including all values and ranges
therebetween

AQ Controlled Release Coat
The AQ controlled release coat is a stable monolithic controlled release coating comprising
15 an aqueous dispersion of a neutral ester copolymer without any functional groups, a poly
glycol having a melting point greater than about 55°C, and one or more pharmaceutically
acceptable excipients; wherein said coating composition is coated onto the dosage form and
cured at a temperature at least equal to or greater than the melting point ofthe poly glycol.
The coating formulation is quite versatile in that it can be used to coat a variety of drug cores
20 and can be easily manipulated to obtain the desired drug release profile.

In certain other embodiments, the AQ controlled release coat comprises an aqueous

46 dispersion of an ethylcellulose, a poly glycol having a melting point greater than about 55°C,

and one or more pharmaceutically acceptable excipients; wherein said coating composition is
25 coated onto the dosage form and cured at a temperature at least equal to or greater than the
melting point ofthe poly glycol. Non limiting examples of aqueous dispersions of an
ethylcellulose include SURELEASEfi (Colorcon, Inc., West Point, Pa., U.S.A.), and
AQUACOATfi (FMC Corp., Philadelphia, Pa., U.S.A.). Combinations are operable.

30 In certain embodiments the AQ controlled release coat is a stable controlled release
monolithic coating that is formed by a process that comprises coating the core with a coating composition to form a coated core with an intermediate coating, and curing the coated core to form the AQ controlled release coat. In at least one embodiment the coating composition

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comprises an aqueous dispersion of a neutral ester copolymer without any functional groups, a poly glycol having a melting point of at least 55°C, and one or more pharmaceutically acceptable excipients. The curing is conducted at a temperature at least equal to or greater
than the melting point ofthe poly glycol. In at least one embodiment the stable AQ
controlled release coat comprises a neutral ester copolymer without any functional groups, a poly glycol having a melting point of at least 55°C, and one or more pharmaceutically
acceptable excipients.

The aqueous dispersion of a neutral ester copolymer without any functional groups can be an
10 ethyl acrylate and methyl methacrylate copolymer dispersion. Non-limiting examples of ethyl
acrylate and methyl methacrylate copolymer dispersions include a 30% aqueous dispersion of
a neutral copolymer based on ethyl acrylate and methyl methacrylate (e.g. EUDRAGITfi NE301)), a 40% aqueous dispersion of a neutral copolymer based on ethyl acrylate and
methyl methacrylate (e.g. EUDRAGITfi NE401)), EUDRAGITfi NM30D, KOLLICOATfi
15 EMM30D, and combinations thereof. in at least one embodiment the neutral ester copolymer
without any functional groups used in the controlled release coating composition is ETJDRAGITfi NE301), EUDRAG1Tfi NE401), or a mixture thereof. The neutral ester
copolymer without any functional groups can be present in certain embodiments in an
amount of from about I % to about 35% by weight ofthe coating composition, including all
20 values and subranges therebetween, depending on the therapeutically active agent used and
the controlled release profile desired. In certain embodiments the neutral ester copolymer
without any functional groups is present in an amount from about 20% to about 99.5% by dry

40 weight ofthe AQ controlled release coat, including all values and subranges therebetween.
In other embodiments the neutral ester copolymer without any functional groups is present in
25 an amount from about 25% to about 60% by dry weight of the AQ controlled release coat,
including all values and subranges therebetween. In still other embodiments the neutral ester
copolymer without any functional groups is present in an amount from about 37% to about
50% by dry weight of the AQ controlled release coat, including all values and subranges
therebetween; for example, including about 38%, about 39%, about 40%, about 41%, about
30 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, and about 4.9%
by dry weight ofthe AQ controlled release coat. In certain embodiments the neutral ester copolymer without any functional groups is present in the coating composition in an amount offrom about 0.4% to about 39.8% by dry weight ofthe tablet including all values and

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subranges therebetween; in other embodiments in an amount offrom about 0.8% to about 24.0% by dry weight ofthe tablet, including all values and subranges therebetween; and in still other embodiments in an amount offrom about 2.0% to about 5.5% by dry weight ofthe tablet, including all values and subranges therebetween.

Hydrophilic agents can also be included in the AQ controlled release coat to promote wetting ofthe coat when in contact with gastrointestinal fluids. Non-limiting examples ofsuch hydrophilic agents include hydrophilic water soluble polymers such as hydroxypropyl methylcellulose HPMC), hydroxypropyl cellulose (HPC) and combinations thereof. In at
10 least one embodiment, HPMC IS the hydrophilic water soluble polymer. If hydrophilic
agents are to be included in the coat composition, the agents can be present in an amount
from about 0.1% to about 10% by weight ofthe coating composition, including all values and ranges therebetween. For example, in certain embodiments the hydrophilic agents are present
in an amount offrom about 0.1% to about 5%, and in other embodiments from about 0.1% to
15 about 3% by weight ofthe controlled release coat composition. in certain embodiments the
hydrophilic agent is present in an amount of from greater than about 0% to about 35% by dry weight ofthe AQ controlled release coat, including all values and subranges therebetween;
preferably from about 8% to about 30% by dry weight ofthe AQ controlled release coat,
including all values and subranges therebetween and still further preferably from about 12%
20 to about 26% by dry weight ofthe AQ controlled release coat, including all values and
subranges therebetween.; In certain embodiments the hydrophilic agent is present in the
coating formulation in an amount of from about 0% to about 14.0% by dry weight ofthe
. tablet, including all values and subranges therebetween; preferably from about 0.2% to about
6.0% by dry weight ofthe tablet, including all values and subranges therebetween; and still
25 further preferably from about 0.8% to about 2.5% by dry weight of the tablet, including all
values and subranges therebetween.

The AQ controlled release coat formulation also comprises a poly glycol with a melting point
of greater than about 55’C. The poly gycol used in the AQ controlled release coat can be a
30 polyethylene glycol with an average molecular weight ranging from about 4,000 daltons to
about 35,000 daltons. Non-limiting examples of a poly gycol with a melting point of greater
than 55°C include polyethylene glycol 4000, polyethylene glycol 4600, polyethylene glycol
6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 12000,

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polyethylene glycol 20000, polyethylene glycol 35000, and mixtures thereof. In certain embodiments, the poly glycol is selected from the group consisting of polyethylene glycol
6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 12000, and mixtures thereof. In at least one embodiment the poly glycol used in the coating composition
51 ofthe AQ controlled release coat is polyethylene glycol 8000. The poly glycol can be present
in certain embodiments in an amount of from about 0.1% to about 10% by weight ofthe
coating composition, including all values and subranges therebetween. In certain
embodiments the poly glycol is present in an amount offrom about 0,5% to about 28% by
dry weight of the AQ controlled release coat, including all values and subranges
10 therebetween. In other embodiments the poly glycol is present in an amount from about 4%
to about 17% by dry weight ofthe AQ controlled release coat, including all values and subranges therebetween. In still other embodiments the poly glycol is present in an amount
from about 7.2% to about 15.2% by dry weight ofthe AQ controlled release coat, including
all values and subranges therebetween; In certain embodiments the poly glycol is present in
15 the coating composition in an amount offrom about 0.1% to about 11.2% by dry weight of
the tablet, including all values and subranges therebetween; in other embodiments in an
amount of from about 0.1% to about 8.0% by dry weight ofthe tablet, including all values
and subranges therebetween; and in still other embodiments in an amount offrom about 0.2%
to about 2.8% by dry weight of the tablet, including all values and subranges therebetween.
20 Other examples ofsuitable polyglycol derivatives having a melting point of at least about
55°C include, but are not limited to, Poloxamer 188, Poloxamer 338, Poloxamer 407, Polyethylene Oxides, Polyoxyethylene Alkyl Ethers, Polyoxyethyleue Stearates and mixtures

46 thereof.

25 In addition to the copolymers and the poly glycol, the AQ controlled release coat formulation
comprises at least one pharmaceutically acceptable excipient. The excipients can include but
are not limited to anti-tacking agents, emulsifying agents, antifoaming agents, flavourants, colourants, and mixtures thereof. It is known in the art that depending on the intended main function, excipients can affect the properties ofthe coat in a series ofways, and many
30 substances used in coat formulations can thus be described as multifunctional. A skilled
worker will know, based on his technical knowledge, which pharmaceutically acceptable excipients are suitable for the desired AQ controlled release coat composition.

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The tackiness of polymeric films is a factor for the coating ofsolid dosage forms and for the subsequent curing step (post coating thermal treatment). During coating with either
cellulosic or acrylic polymers, sometimes an unwanted agglomeration ofseveral granules or beads can occur, for example at higher product processing temperatures. Accordingly, the
5 addition of anti-tacking agents to coating formulations can be desirable in certain
embodiments. The anti-tacking agents which can be used in certain embodiments include but
are not limited to adipic acid, magnesium stearate, calcium stearate, zinc stearate,
hydrogenated vegetable oils, sterotex, glyceryl monostearate, talc (e.g. talc 400), sodium benzoate, sodium lauiyl sulfate, magnesium lai.iryl sulfate, and mixtures thereof. In at least
10 one embodiment, talc is the anti-tacking agent. Talc can also function as a wetting agent.
Mixtures ofthe anti-tacking agents are operable. The amount of anti-tacking agent in the controlled release coat composition can range from about 1% to about 15% by weight ofthe controlled release coating composition, including all values and ranges therebetween. For example, in certain embodiments the anti-tacking agent is present in an amount of from about
15 1% to about 7% by weight ’ofthe controlled release coating composition. In certain
embodiments the anti-tacking agent is present in an amount of from greater than about 0% to about 50% by dry weight ofthe AQ controlled release coat including all values and
subranges therebetween; preferably from about 2% to about 40% by dry weight ofthe AQ controlled release coat including all values and subranges therebetween and still further
20 preferably from about 10% to about 30% by dry weight of the AQ controlled release coat
including all values and subranges therebetween. In certain embodiments the anti-tacking
agent is present in the coating formulation in an amount of from about 0% to about 20.0% by
dry weight ofthe tablet, including all values and subranges therebetween; in other
embodiments in an amount of from about 0% to about 12.0% by dry weight ofthe tablet,
25 including all values and subranges therebetween.; and in still other embodiments in an amount
offrom about 0.6% to about 7.0% by dry weight ofthe tablet, including all values and
subranges therebetween.

Certain embodiments can include anti-foaming agents in the AQ controlled release
30 coat composition. Non-limiting examples of useful anti-foaming agents include silicon oil,
simethicone, and mixtures thereof. In at least one embodiment, simethicone is the anti-foaming agent used in the AQ controlled release coat composition. The anti-foaming agent
can be present in an amount of up to about 0.5% by weight ofthe AQ controlled release coat

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composition. For example, in certain embodiment the anti-foaming agent is present in an amount of from about 0.1% to about 0.4% by weight of the AQ controlled release coat composition, including all values and ranges therebetween. In certain embodiments the anti-foaming agent is present in an amount of from greater than about 0% to about 3% by dry
5 weight of the AQ controlled release coat, including all values and subranges thoiebetween.
In other embodiments the anti-foaming agent is present in an amount from about 0.4% to about 2% by dry weight of the AQ controlled release coat, including all values and subranges therebetween. In still other embodiments the anti-foaming agent is present in an amount from about 0.8% to about 1.5% by dry weight of the AQ controlled release coat, including all
10 values and subranges therebetween; for example, including about 0.9%, about 1.0%, about
1.1%, about 1.2%, about 1.3%, and about 1.4% by dry weight of the AQ controlled release coat. In certain embodiments the anti-foaming agent is present in the coating formulation in
an amount of from about 0% to about 1.2% by dry weight of the tablet, including all values and subranges therebetween; in other embodiments in an amount of from about 0% to about
15 0.8% by dry weight ofthe tablet, including all values and subranges therebetween; and in still
other embodiments in an amount of from about 0% to about 0.2% by dry weight ofthe tablet, including all values and subranges therebetween; for example, including about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0.07%, about 0.08%, about 0.09%, about 0.10%, about 0.11%, about 0.12%, about 0.13%, about 0.14%, about
20 0.15%, about 0.16%, about 0.17%, about 0.18%, and about 0.19% by dry weight ofthe tablet.

Certain embodiments can include emulsifying agents (also called emulsifiers or emirigents) in
the AQ controlled release coat. Emulsifying agents can facilitate emulsification during
25 manufacture of the AQ controlled release coat, and also provide emulsion stability during the
shelf-life of the product. Non-limiting examples of emulsifying agents include naturally occurring materials and their semi synthetic derivatives, such as the polysaccharides, as well
as glycerol esters, cellulose ethers, sorbitan esters and polysorbates. Mixtures are operable.
In at least one embodiment the emulsifying agent is Polysorbate 80 polyoxyethylene sorbitan
30 mono-oleate) (e.g. TWEENfi 80). The emulsifying agent can be present in an amount of
from about 0% to about 0.5% by weight of the AQ controlled release coat composition, including all values and subranges therebetween. For example, in certain embodiments the emulsifying agent is present in an amount of from about 0.1% to about 0.3% by weight ofthe

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AQ controlled release coat composition, including all values and ranges therebetween. In certain embodiments the emulsifying agent is present in an amount of from greater than about 0% to about 2% by dry weight of the AQ controlled release coat, including all values and subranges therebetween. In other embodiments the emulsifying agent is present in an amount
5 from about 0.1% to about 1% by dry weight of the AQ controlled release coat, including all
values and subranges therebetween. In still other embodiments the emulsifying agent is present in an amount from about 0.25% to about 0.75% by dry weight of the AQ controlled release coat, including all values and subranges therebetween; for example, including about 0.30%, about 0.35%, about 0.40%, about 0.45%, about 0.50%, about 0.55%, about 0.60%,
10 about 0.65%, and about 0.70% by dry weight of the AQ controlled release coat. In certain
embodiments the emulsifying agent is present in the coating formulation in an amount of from greater than about 0% to about 0.8% by dry weight of the tablet, including all values
and subranges therebetween; in other embodiments in an amount of from greater than about
0% to about 0.4% by dry weight of the tablet, including all values and subranges
15 therebetween; and in still other embodiments in an amount of from greater than about 0% to
about 0.2% by dry weight of the tablet, including all values and subranges therebetween; for example, including about 0.01%, about 0.02%, about 0.03%, about 0.04%, about 0.05%, about 0.06%, about 0,07%, about 0.08%, about 0.09%, about 0.10%, about 0.11%, about 0.12%, about 0.13%, about 0.14%, about 0.15%, about 0.16%, about 0.17%, about 0.18%,
20 and about 0.19% by dry weight ofthe tablet.

Certain embodiments can include colorants in the film coat formula. Such colorants can be water-insoluble colors (pigments). Pigments have certain advantages over water-soluble colors in that they tend to be more chemically stable towards light, provide better opacity and
25 covering power, and optimize the impermeability of a given film to water vapor. Non-
limiting examples of suitable colorants include iron oxide pigments, titanium dioxide, and aluminum Lakes. Mixtures are operable. In at least one embodiment the pigment is titanium dioxide. The pigment or colorant can be present in an amount of from about 0.1% to about 10% by weight of the AQ controlled release coat composition, including all values and
30 ranges therebetween. For example, in certain embodiments the pigment or colorant is present
in an amount of from about 0.1% to about 5%, and in other embodiments from about 0.1% to about 2% by weight of the AQ controlled release coat composition. In certain embodiments
the colorant is present in an amount of from greater than about 0% to about 20% by dry

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weight of the AQ controlled release coat, including all values and subranges therebetween.
In other embodiments the colorant is present in an amount from greater than about 0% to about 10% by dry weight of the AQ controlled release coat, including all values and subranges therebetween. In still other embodiments the colorant is present in an amount from
5 about 2.2% to about 6.2% by thy weight of the AQ controlled release coat, including all
values and subranges therebetween. In certain embodiments the colorant is present in the coating formulation in an amount of from greater than about 0% to about 8.0% by dry weight
of the tablet, including all values and subranges therebetween; in other embodiments in an amount of from greater than about 0% to about 5.0% by dry weight ofthe tablet, including all
10 values and subranges therebetween; and in still other embodiments in an amount of from
greater than about 0% to about 1.0% by dry weight of the tablet, including all values and subranges therebetween; for example, including about 0.1%, about 0.2%, about 0.3%, about

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0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, and about 09% by dry weight ofthe tablet.

In at least one embodiment, the AQ controlled release coat hydrates when placed into
water. In at least one embodiment the dosage form that is coated with the AQ controlled release coat floats in water. In at least one embodiment, the controlled release dosage form, upon oral administration to a patient, provides controlled release of an effective amount of
20 the bupropion hydrobromide to at least one region of the patient’s upper gastrointestinal tract
(e.g. the stomach).

In certain embodiments the AQ controlled release coat is formed by a process that
does not involve the use of an organic solvent. In such embodiments the AQ controlled
25 release coat composition is aqueous based and not solvent based, in contrast to prior art

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coating compositions that are solvent based (e.g. "PharmaPASS" composition).

In certain embodiments the AQ controlled release coat ofthe bupropion hydrobromide tablet
can be made according to any one ofthe methods described herein.

The AQ controlled release coat can be applied onto a core comprising an effective amount of
the bupropion hydrobromide salt by a process which involves the atomization (spraying) of
the coating solution or suspension onto a bed of the tablet cores. Some examples of

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equipment suitable for film coating include: ACCELA COTAfi (Manesty Machines, Liverpool, UK), HI-COATERfi (Freund Company, Japan), DRTACOATERTM (Driam Metallprodukt GmbH, Germany), HTF/150 (GS, Italy), and IDATM (Dumoulin, France). Examples ofunits that function on a fluidized-bed principle include: AEROMATICTM
(Fielder, Switzerland and UK) and GLATTTM AG (Switzerland). In at least one embodiment,
the apparatus used for film coating is the ACCELA COTAfi.

The coating fluid can be delivered to the coating apparatus from a peristaltic pump at the
desired fate and sprayed onto the rotating or fluidizing tablet cores. The tablet cores are pre-
10 warmed to about 30°C. During the coating process, the product temperature range is
maintained at from about 25°C to about 35°C by adjusting the flow rate ofthe inlet and outlet
air, temperature ofthe inlet air and spray rate. A single layer of coat is applied and once
spraying is complete, the coated tablet cores are dried from. about 30°C to about 40°C for a
time period offrom about 3 to about 5 minutes at a low pan speed and low air flow. The pan
15 is readjusted to jog speed, and drying continues for a time period of from about 12 to about
15 minutes.

The coated tablet cores are placed onto a tray and cured (post coating thermal treatment) in an electrical or steam oven at a temperature above the temperature ofthe melting point ofthe
20 polyethylene glycol or derivative thereof. In certain embodiments the curing temperature is
greater than the melting point ofthe polyethylene glycol or derivative thereof. In certain embodiments the curing time is from about 2 to about 7 hours. The cured coated tablets are

46 subsequently cooled to room temperature.

25 The AQ controlled release coat is quite versatile. The length and time for the delay can be
controlled by rate of hydration and the thickness ofthe coat. The drug release rate
subsequent to the delay can be determined by the thickness and permeability ofthe hydrated coat, Thus, it is possible to regulate the rate of hydration and permeability ofthe AQ
controlled release coat so that the desired controlled-release drug profile can be achieved.
30 There is no preferred coat thickness, as this will depend on the controlled release profile
desired. Other parameters in combination with the thickness of the coat include varying the concentrations of some ofthe ingredients ofthe stable coat composition ofthe invention described and/or varying the curing temperature and length of curing the coated tablet cores.

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The skilled artisan will know which parameters or combination ofparameters to change for a desired controlled release profile.

As will be seen from the non-limiting examples described herein, the coatings used in certain
5 embodiments ofthe present invention are quite versatile. For example, the length and time
for the lag time can be controlled by the rate of hydration and the thickness ofthe controlled release coat. Other parameters in combination with the thickness ofthe coatings include
varying the concentrations ofsome ofthe ingredients of the coating compositions of certain embodiments described and/or varying the curing temperature and length of curing the coated
10 tablet cores. The skilled artisan will know which parameters or combination ofparameters to
change for a desired controlled release profile,

The Moisture Barrier Coat

In certain embodiments, an optional moisture barrier is applied directly onto the controlled
15 release coat In other embodiments a moisture barrier coat is not included in the dosage form.
In certain embodiments the moisture barrier comprises an enteric polymer (e.g. acrylic
polymer), a permeation enhancer and optionally a plasticizer.

In certain embodiments, the enteric polymer is an acrylic polymer. For example, the acrylic
20 polymer can be a methacrylic acid copolymer type C [poly(methacrylic acid, methyl
methacrylate) 1:1] (e.g. EUDRAGITfi L 30 D-55). The methacrylic acid copolymer can be present in an amount, which can vary from about 1% to about 3% ofthe tablet dry weight including all values and ranges therebetween and from about 55% to about 70% ofthe
moisture barrier dry weight including all values and ranges therebetween. For the 174 mg
25 dose ofthe extended release tablet of certain embodiments ofthe present invention, the
methacrylic acid copolymer can vary from about 2% to about 3% ofthe tablet dry weight including all values and ranges therebetween. For example in the 174mg tablet of certain embodiments, the amount ofmethacrylic acid copolymer is present in an amount of about
2.5% ofthe tablet dry weight. With respect to the moisture barrier itself, the amount of the
30 methacrylic acid copolymer in the 174 mg tablet can be present in an amount of from about
55% to about 70% by weight ofthe moisture barrier dry weight including all values and
ranges therebetween. For example, in the 174mg tablet of certain embodiments the
methacrylic acid copolymer is present in an amount of about 60% ofthe moisture barrier dry

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weight. Forthe 348 mg dose ofthe extended release tablet of certain embodiments, the amount ofthe methacrylic acid copolymer can vary from about 1.5% to about 3% ofthe
tablet dry weight including all values and rangcs therebetween. For example, in the 348mg tablet of certain embodiments, the amount ofmethacrylic acid copolymer is present at an
5 amount of about 2% by weight ofthe tablet dry weight. With respect to the moisture barrier
itself, the methacrylic acid copolymer in the 348 mg tablet typically will be present in an
amount offrom about 55% to about 70% ofthe moisture barrier dry weight including all
values and ranges therebetween. For example in certain embodiments ofthe 348mg tablet the methacrylic acid copolymer is present in an amount of about 60% ofthe moisture barrier dry
10 weight. For the 522 mg, dose ofthe extended release tablet of certain embodiments, the
amount ofthe methacrylic acid copolymer can vary from about 0.5% to about 5% ofthe
tablet dry weight including all values and ranges therebetween. For example, in the 522mg tablet of certain embodiments, the amount ofmethacrylic acid copolymer is present at about
2% by weight ofthe tablet dry weight. With respect to the moisture barrier itself, the
15 methacrylic acid copolymer in the 522 mg tablet typically will be present in an amount of
from about 40% to about 80% ofthe moisture barrier dry weight. For example, in certain
embodiments ofthe 522 mg tablet the methacrylic acid copolymcr is present in an amount of
about 65% ofthe moisture barrier dry weight.

20 It is known in the art that methacrylic acid copolymers can become brittle, and that coatings
that contain methacrylic acid copolymers could be made more elastic and pliable by the
addition of a plasticizer. In certain embodiments the moisture barrier coat comprises a

40 plasticizer. Non-liimting examples ofplasticizers useful for the moisture barrier coat of

certain embodiments include acetylated monoglycerides; acetyltributyl citrate, butyl phthalyl
25 butyl glyco late; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl phthaiyl ethyl
glycolate; glycerin; propylene glycol; triacetin; tripropioin; diacetin; dibutyl phthalate; acetyl monoglyceride; acetyltriethyl citrate, polyethylene glycols; castor oil; rape seed oil, olive oil,
sesame oil, triethyl citrate; polyhydric alcohols, glycerol, glycerin sorbitol, acetate esters,
gylcerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl
30 phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidized tallate,
triisoctyl trimellitate, diethylhexyl phthalatc, di-n-octyl phthalate, di-i-octyl phthalate, di4-
decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethyll’iexyl azelate, dibutyl sebacate,

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diethyloxalate, diethylmalate, diethylfumei ate, dibutylsuccinate, diethyhnalouate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, and mixtures thereof, polyols (e.g. polyethylene glycol) of various molecular weights, and mixtures thereof. In certain embodiments, the plasticizer in the moisture barrier coat comprises a combination oftriethyl
5 citrate and polyethylene glycol 4000 (e.g. CARBOWAXfi 4000). In certain ofthese
embodiments, the ratio oftriethyl citrate to polyethylene glycol 4000 is about 1:2. The
plasticizer can be present in the moisture barrier coat of certain embodiments in an amount
which can vary from about 0.2% to about 0.5%, including all values and ranges therebetween (e.g, including about 0.3%, and about 0.4% of the tablet dry weight). For example in certain
10 embodiments the plasticizer can be present in an amount of about 0.35% ofthe tablet dry
weight for a 174 mg tablet; in an amount of from about 0.2% to about 0.4% ofthe tablet dry weight for a 348 mg tablet; and in an amount of from about 0.05% to about 0.5% ofthe tablet dry weight for a 522 mg tablet, including all values and ranges therebetween. With respect to
the moisture barrier itself, the plasticizer if present in certain embodiments can be present in
15 an amount of from about 1% to about 30% by weight ofthe moisture barrier dry weight,
including all values and ranges therebetween. For example, in certain embodiments the
plasticizer is present in an amount of from about 10% to about 14% ofthe moisture barrier
dry weight for the 174 mg, 348 mg and 522 mg dose extended release tablet ofthe present invention. It is well known in the art that depending on the intended main function,
20 excipients to be used in tablets are subcategorized into different groups. However, one
excipient can affect the properties of a drug or the tablet as a whole in a series ofways, and many substances used in tablet formulations can therefore be described as multifuncional.
For example, the polyethylene glycol used in the plasticizer combination for the moisture
barrier can serve not only to increase the hydrophilicity ofthe moisture barrier, but can also
25 act as a glidant.

In certain embodiments the moisture barrier can further comprise a permeation enhancer that
can Increase its hydrophilicity, and can also act as a glidant. The permeatioti enhancer can be
a hydrophilic substance and can be selected from the following non-limiting examples:
30 hydrophilic polymers such as hydroxypropylmetihylcellulose, cellulose ethers and protein-
derived materials ofthese polymers, the cellulose ethers, such as hydroxyalkylcelluloses, carboxyalkylcelluloses, and mixtures thereof. Also, synthetic water-soluble polymers can be used, such as polyvinylpyrrolidone, cross-linked polyvinyl-pyrrolidone, polyethylene oxide,

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water-soluble polydextrose, saccharides and polysaccharides, such as pullulan., dextran, sucrose, glucose, lactose, fructose, mannitol, mannose, galactose, sorbitol and mixtures thereof. In at least one embodiment ofthe present invention, the hydrophilic polymer comprises hydroxypropyl-methylceliulose. Other non-limiting examples of permeation
5 enhancers that can be used in the moisture barrier of certain embodiments include alkali
metal salts such as aluminum oxidelithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, and mixtures thereof. The permeation enhancers or pore-formers, can also be polymers
which are soluble in the environment ofuse, such as CARBOWAXfi, CARBOPOLfi, and
10 mixtures thereof. Non-limiting examples ofpore formers include diols, polyols, polyhydric
alcohols, polyalkylene glycols, po lyglycols, poly(a-w)alkylenediols, and mixtures thereof.
Other permeation enhancers which can be useful in the formulations ofthe present invention include starch, modified starch, and starch derivatives, gums, including but not limited to xanthan gum, alginic acid, other alginates, benitonite, veegum, agar, guar, locust bean gum,
15 gum arabic, quince psyllium, flax seed, okra gum, arabinoglactin, pectin, tragacanth,
selerogiucan, dextran, arnylose, amylopectin, dextrin, cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambda-carrageenan, gum karaya, biosynthetic gum, and mixtures thereof. Other permeation enhancers include materials useful for making microporous lamina in the environment of use,
20 such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate
groups reoccur in the polymer chain, microporous materials such as bisphenol, a microporous poly(vinylchloride), micro-porous polyamides, microporous modacrylic copolymers,
microporous styrene-acrylic and its copolymers, porous polysulfones, halogenated poly(vinylidene), polychioroethers, acetal polymers, polyesters prepared by esterification of a
25 dicarboxylic acid or anhydride with an alkylene polyol, poly(allcylenesulfides), phenolics,
polyesters, asymmetric porous polymers, cross-linked olefin polymers, hydrophilic
microporous bomopolymers, copolymers or interpolymers having a reduced bulk density, and other similar materials, poly(urethane), cross-linked chain-extended poly(urethane),
poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked
30 poly(vinylpyrrolidone), silicon dioxide, colloidal silica, microcrystalline cellulose and any
combination thereof. In at least one embodiment ofthe invention the permeation enhancer is silicon dioxide (e.g. SYLOIDfi 244FF). The amount of permeation enhancer can vary from about 0.5% to about 1% by weight ofthe tablet dry weight including all values and ranges

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therebetween and from about 25% to about 30% by weight ofthe moisture barrier dry weight including all values and ranges theiebetween. For the 174 rng dose extended-release tablet or the 348 mg dose extended-release tablet of certain embodiments ofthe invention, the
permeation enhancer can be present in an amount of about 0.5% to about 2% of the tablet dry
5 weight including all values and ranges therebetween and from about 20% to about 40% by
weight ofthe moisture barrier dry weight including all values and ranges therebetween For example, in certain embodiments ofthe 174mg dose tablet, the permeation enhancer is
present in an amount offrom about 25% to about 30% by weight of the moisture barrier dry weight. For the 348 mg dose extended release tablet ofthe invention, the permeation
10 enhancer can be present in an amount which can vary from about 0.5% to about 2% by
weight ofthe tablet dry weight, and from about 20% to about 40% by weight ofthe moisture barrier dry weight. For example, in certain embodiments ofthe 348 mg dose tablet, the permeation enhancer is present in an amount offrom about 25% to about 30% by weight of
the moisture barrier dry weight For the 522 mg dose extended release tablet ofthe invention,
15 the permeation enhancer can be present in an amount which can vary from about 0.1 % to
about 2% by weight ofthe tablet dry weight including all values and ranges therebetween,
and from about 20% to about 40% by weight ofthe moisture barrier dry weight including all values and ranges therebetween. For example, in certain embodiments ofthe 522 mg dose
tablet, the permeation enhancer is present in an amount of from about 25% to about 30% by
20 weight ofthe moisture bather dry weight.

In at least one embodiment ofthe invention, the ratio ofthe methacrylic acid copolymer:plasticizer:permeation enhancer in the moisture barrier is about 13:2:5.

25 In certain embodiments the moisture barrier ofthe.bupropion hydrobromide dosage form can
be made according to any one ofthe methods described herein.

The preparation and application ofthe moisture barrier process can be as follows. The
optional plasticizer (e.g. a combination of polyethylene glycol 4000 and triethyl citrate), can
30 be first added to water and the mixture mixed to homogeneity. The methacrylic acid co-
polymer (e.g. EUDRAGITfi L 30 D55), is next sieved and added to the plasticizer mixture
and mixed to homogeneity. In a separate container the permeation enhancer (e.g. silicon dioxide) is dissolved in water until a homogeneous mixture is achieved. The plasticizer and

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methacrylic acid copolymer mixture is then combined with the permeation enhancer solution and mixed to homogeneity. The resulting moisture barrier solution is then sprayed onto the tablet cores coated with the controlled release coat using a tablet coater, fluidized bed
apparatus or any other suitable coating apparatus known in the art until the desired weight
gain is achieved. The tablets coated with the moisture barrier are subsequently dried prior to packaging.

The moisture barrier is applied to the controlled release coated tablet cores such that the
weight gain is not more than about 6% of the tablet dry weight for the 174 mg, 348 mg and
10 522 mg extended release tablets of certain embodiments ofthe present invention. In certain
embodiments the weight gain is not more than about 3.5% ofthe tablet dry weight for the 174 mg, 348 mg and 522 mg extended release tablets. The amount ofthe moisture barrier applied typically does not significantly render the extended release tablet described herein more
resistant to gastric fluid. However, in certain embodiments the moisture barrier can have an
15 impact on the drug release characteristics.

The moisture barrier as used in certain embodiments, does not function as an enteric coat.
Even though the methacrylie acid copolymer, EUDRAGITfi L 30 D-55, is referenced and is
used in enteric coating formulations in the art, its functionality is formulation dependent and
20 on the quantity ofthe material applied. As is known in the art, an enteric coating is applied
where a drug may be destroyed or inactivated by gastric juice or where the drug may irritate
the gastric mu.cosa. To meet the requirements for an enteric coat, the test as described in the
. USP (method A or B) stipulates that after 2 hours in acidic media (e.g. 0.1N HC1), no
individual values of at least six experiments exceed about 10% ofthe active drug dissolved
25 and not less than about 75% dissolved at about 45 minutes in pH about 6.8. The moisture
barrier of certain embodiments does not meet this requirement for the following reasons even
though the bupropion hydrobromide salt is not negatively affected in acidic media nor is it
irritating the gastric mucosa: (1) to obtain enteric integrity with a film containing
EUDRAGITfi L 30 D-55, a weight gain of from about 6% to about 8% based on the dry
30 polymer per dosage unit is recommended. The amount of EUDRAGITfi L 30 D-55 solid
applied onto the controlled release coated tablet cores is not more than about 6%, and in at
least one embodiment, is not more than about 3%, (2) if enteric integrity would be required,
the dissolution test for the finished product (i.e., the moisture barrier coated tablet cores) at

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the 2 hour time point would not stipulate a limit of no more than about 20%, and (3) analytical tests performed on these coatings indicate that the coatings do not meet all the test requirements as an enteric coated product as defined by USP test methods.

The XL tablet of certain embodiments of the invention provides an extended release ofthe bupropion hydrobromide salt. In at least one embodiment no pore forming agent is present in
the XL coating formulation. An extended release bupropion hydrobromide formulation is
provided in certain embodiments such that after about 2 hours, not more than about 20% of
the bupropion hydrobrornide content is released. For example, in certain embodiments, from
10. about 2% to about 18%, preferably from about 4% to about 8%, or about 5% ofthe
bupropion hydrobromide content is released after about 2 hours. After about 4 hours, from

18 about 15% to about 45% ofthe bupropion hydrobromide content is released. For example, in
certain embodiments from about 21% to about 37%, more preferably from about 28% to
about 34%, or about 32%of the bupropion hydrobroniide content is released after about 4
15 hours. After about 8 hours, about 40% to about 90% ofthe bupropion hydrobromide content
is released. For example, in certain embodiments from about 60% to about 85%, from about
68% to about 74%, or about 74% ofthe bupropion hydrobromide content is released after
about 8 hours. After about 16 hours not less than about 80% ofthe bupropion hydrobromide content is released. For example, in certain embodiments ofthe bupropion hydrobromide
20 content is released after about 16 hours.

Also, extended release tablets are provided in certain embodiments wherein after about 2
hours not more than about 40% (e.g., about 33%) ofthe bupropion hydrobromide is released; after about 4 hours from about 40 to about 75% ofthe bupropion hydrobromide is released
25 (e.g., about 59%); after about 8 hours at least about 75% ofthe bupropion hydrobromide is
released (e.g., about 91%),- and after about 16 hours at least about 85% ofthe bupropion hydrobromide is released (e.g., about 97%). In all instances herein when actual or prophetic dissolution profiles are provided this means that the medicament possesses such a profile in at least one dissolution medium under prescribed conditions such as are identified herein and
30 are well known to those skilled in the art. Such dissolution media, dissolution conditions and
apparatus for use therein are disclosed in the United States Pharmacopoeia (LISP) and
European and Japanese counterparts thereof. Additionally, specific examples thereof are provided in this application.

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Enhanced Absorption (EA) Tablets

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In certain embodiments ofthe present invention, there is provided an enhanced absorption
(EA) tablet having a core comprising a bupropion hydrobromide salt and conventional
5 excipients, wherein the bupropion hydrobromide salt provides for the reduction ofincidences
of and/or severity of bupropion-induced seizures, and is more stable, as compared with
equivalent molar amounts ofbupropion hydrochloride. The core is surrounded by an EA coating, which controls the release ofthe bupropion hydrobromide salt. In certain
embodiments, the EA coating consists of one coat. An advantage ofthe EA tablet includes
10 the lower amount of drug required in the composition to be an effective amount, which in
turn can lead to a reduction ofside effects. The EA tablet optionally can comprise one or
more additional functional or non-functional coats surrounding the core or EA coating.

The EA Core

15 The core ofthe EA tablet comprises an effective amount of a bupropion hydrobromide salt, a
binder and a lubricant, and can contain other conventional inert excipients. In certain embodiments the core ofthe EA tablet can comprise the same excipients as, and can be processed in the same manner as the core of the extended release tablet. The amount ofthe bupropion hydrobromide salt present in the EA core can vary from about 40% to about 99%
20 by weight ofthe EA tablet dry weight, including all values and ranges therebetween. The EA
tablet comprises an effective amount of bupropion hydrobromide salt that can vary from
about 50mg to about 1000mg, including 100, 150, 200, 250, 300, 350, 400, 450, 500, 510,
520, 530, 540, 550, 560, 570, 580, 590, 600, 650, 700, 750, 800, 85, 900, 950 mg and all
values and ranges therebetween. For example, certain embodiments ofthe EA tablet can
25 comprise about 150mg, about 300mg or about 450mg of bupropion hydrobromide. For a
150mg dose tablet the bupropion hydrobromide can be present in an amount of from about
76% to about 84% by weight ofthe tablet dry weight. For a 300 mg dose, the amount of bupropion hydrobromide can be present in an amount of from about 80% to about 83% by weight ofthe tablet dry weight. For a 450 mg dose, the amount of bupropion hydrobromide
30 can be present in an amount offrom about 75% to about 90% by weight ofthe tablet dry
weight. For the 150mg, 300mg and 450mg dose bupropion hydrobromide EA tablets of
certain embodiments ofthe invention, the amount ofbupropion hydrobromide can be present
at about 94% by weight ofthe dry core for each dose.

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The EA Tablet Coating

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The EA tablet cores can be coated in one stage. The EA coating is applied directly onto the surface ofthe tablet cores and functions to control the release ofthe bupropion hydrobromide salt. The EA coating is a semi-permeable coat comprising a water-insoluble, water-
permeable film-forming polymer, a water-soluble polymer, and optionally a plasticizer. In
certain embodiments the EA coating can comprise the same ingredients as, and can be
processed in the same manner as the XL controlled release coat.

10 Non-limiting examples ofwater-insoluble, water-permeable film-forming polymers useful for
the EA coating include those that can be used in the XL controlled release coat. The amount ofthe water-insoluble water-permeable film-forming polymer can vary from about 1% to
about 8% by weight ofthe tablet dry weight, including all values and ranges therebetweell.
For example, in certain embodiments the amount ofthe water-insoluble water-permeable
15 film-forming polymer is from about 2% to about 6% by weight ofthe tablet dry weight. For
certain embodiments ofthe 150mg, 300mg or 450mg dose EA tablets of certain embodiments ofthe invention, the amount of water-insoluble water permeable film-forming polymer is
from about 1% to about 15% by weight ofthe tablet dry weight. For example, in certain embodiments of the 150mg dose EA tablets, the amount ofthe water-insoluble water-
20 permeable film-forming polymer is present at about 10.5% by weight ofthe tablet dry weight.
With respect to the EA coat itself:, the amount of water-insoluble water-permeable film-
forming polymer in certain embodiments ofthe 150mg dose EA tablets is from about 35% to about 60% by weight ofthe EA coat dry weight. For example, in certain embodiments ofthe 150mg dose EA tablet, the amount of water-insoluble water-permeable polymer is present at
25 about 55% by weight ofthe EA coat dry weight. For certain embodiments of the 300 mg
dose EA tablet ofthe invention, the amount of water-insoluble water-permeable film-forming polymer is from about 1% to about 8% by weight of the tablet dry weight. For example, in certain embodiments ofthe 300mg dose EA tablet, the amount ofwater-insoluble water-permeable film forming polymer is present at about 6.3% by weight ofthe tablet dry weight.
30 With respect to the EA coat itself, the water-insoluble water-permeable film-forming polymer
in the 300mg dose EA tablet can be present in an amount of about 55% by weight ofthe EA coat dry weight. For certain embodiments ofthe 450mg dose FA tablet ofthe invention, the amount ofwater-insoluble water-permeable film-forming polymer is from about 0.5% to

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about 10% by weight of the tablet dry weight, and in other embodiments is from about 1% to about 6% by weight ofthe tablet dry weight. With respect to the BA coat itself, the water-insoluble water-permeable film-forming polymer in the 450mg dose EA tablet can be present
in an amount of about 37% by weight ofthe EA coat dry weight.

In certain embodiments, the EA coat further comprises a plasticizer. Non-limiting examples ofplasticizers that can be used in the EA coat include those that can be used in the XL
controlled release coat. The amount of plasticizer that can be used in the BA coat can vary in
an amount from about 0.5% to about 4% by weight ofthe tablet dry weight, including all
10 values and ranges therebetween. In a further embodiment ofthe invention, when a mixture of
two plasticizers is used, the ratio ofthe two plasticizers can range from about 5:95 to about
95:5, including all values and ranges therebetween. In at least one embodiment ofthe
invention, the plasticizer is polyethylene glycol 4000, dibutyl sebacate, or a mixture thereof.
The ratio ofpolyethylene glycol 4000:dibutyl sebacate can range from about 5:95 to about
15 95:5. For certain embodiments ofthe 150 mg dose EA tablet ofthe invention, the amount of
plasticizer present in the BA coat is from about 0.5% to about 4% by weight ofthe tablet dry weight. For example, in certain embodiments of the 150 mg dose EA tablet, the amount of
plasticizer is present at about 3.1% by weight ofthe tablet dry weight. For certain
embodiments ofthe 300 mg dose EA tablet of the invention, the amount ofplasticizer present
20 is from about 0.5% to about 3% by weight ofthe tablet dry weight. For example, in certain
embodiments ofthe 300 mg dose BA tablet, the amount of plasticizer is present at about 2.0%
by weight ofthe tablet dry weight. For certain embodiments ofthe 450 mg dose EA tablet of
. the invention, the amount ofplasticizer present is from about 0.5% to about 4% by weight of
the tablet dry weight. For certain embodiments ofthe 150 mg, 300 mg and 450 mg dosage
25 forms, the plasticizer is present in an amount offrom about 6% to about 30% by weight of
the EA coat dry weight. For example, in certain embodiments the amount ofplasticizer is
present at about 17% by weight of the BA coat dry weight

Non-limiting examples ofwater-soluble polymers useful for the EA coat include those that
30 can be used in the XL controlled release coat. In at least one embodiment ofthe invention,
the water-soluble polymer is polyvinylpyrrolidone (e.g. Povidonefi USP) the amount of
which can vary from about 1.5% to about 10% by weight ofthe tablet dry weight, including
all values and ranges therebetween. With respect to the EA coat itself, the amount of water-

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soluble polymer present can vary from about 20% to about 50% by weight ofthe BA coat thy weight. For certain embodiments ofthe 150 mg dose ofthe EA tablet of the invention, the amount of water-soluble polymer present is from about 1.5% to about 10% by weight ofthe tablet dry weight or from about 20% to about 50% by weight ofthe EA coat dry weight. For
5 example, in certain embodiments ofthe 150 mg dose EA tablet, the water-soluble polymer is
present in an amount of about 28% by weight of the EA coat dry weight. For certain embodiments ofthe 300 mg: dose ofthe EA tablet ofthe invention, the amount ofwater-
soluble polymer present is from about 1.5% to about 10% ofthe tablet dry weight and from about 20% to about 50% by weight ofthe BA coat dry weight. For example, in certain
10 embodiments ofthe 300 mg dose EA tablet, the water-soluble polymer is present in an
amount of about 28% by weight of the BA coat dry weight. For certain embodiments ofthe
450 mg dose of the BA tablet ofthe invention, the amount of water-soluble polymer present
is from about 2% to about 5% ofthe tablet dry weight and from about 40% to about 50% by weight ofthe EA coat dry weight.
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The ratio ofwater-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer for the BA tablet coating typically will vary from about 3:1:4 to about 5:1:2,
including all values and ranges therebetween. For example in certain embodiments the ratio ofwater-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer
20 for the BA tablet coating is about 4:1:3. In at least one embodiment ofthe BA tablet coating,
the ratio ofthe water-insoluble water-impermeable film-forming polymer:plasticizer:water-soluble polymer is from about 7:2:6 to about 19:5:18, and in another embodiment is about 13:4:12. In at least one embodiment ofthe 450mg dosage form, the ratio of water-insoluble water-permeable film forming po1ymer:plasticizer:water-solubl polymer for the BA coating
25 is about 13:6:16.

In certain embodiments the EA coat ofthe bupropion hydrobromide dosage form can be
made according to any one ofthe methods described for the XL controlled release coat.

30 Depending on the dissolution or in-viva release profile desired, the weight gained after
coating the tablet core with the BA coat can vary from about 3% to about 30% ofthe weight ofthe dry tablet core, including all values and ranges therebetween. For certain embodiments ofthe 150 mg dose BA tablet ofthe invention the weight gain is from about 8% to about 20%

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ofthe weight ofthe dry tablet core. For example, in certain embodiments ofthe 150 mg dose EA tablet, the weight gain is about 14% of the weight ofthe dry tablet core. For certain embodiments ofthe 300 mg dose EA tablet ofthe invention the weight gain is from about
10% to about 15% ofthe weight ofthe dry tablet core. For example, in certain embodiments ofthe 300mg dose EA tablet, the weight gain is about 13% ofthe weight ofthe dry tablet core. For certain embodiments ofthe 450 mg dose EA tablet ofthe invention the weight gain is from about 5% to about 15% ofthe weight ofthe dry tablet core. For example, in certain embodiments ofthe 450mg dose EA tablet, the weight gain is about 8.5% ofthe weight ofthe dry tablet core.

The EA tablet provides an enhanced-absorption of the bupropion hydrobromide salt wherein typically no pore forming agent is present in the formulation. An enhanced absorption
bupropion hydrobromide formulation is provided such that after about 2 hours, not more than about 25% ofthe bupropion hydrobromide content is released. For example, in certain
15 embodiments from about 10% to about 20% ofthe bupropion hydrobromide content is
released after about 2 hours. After about 4 hours, from about 25% to about 55% ofthe bupropion hydrobromide content is released. For example, in certain embodiments from
about 30% to about 50% ofthe bupropion hydrobromide content is released after about 4
hours. After about 8 hours, more than about 60% ofthe bupropion hydrobromide content is
20 released. For example, in certain embodiments from about 70% to about 90% ofthe

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bupropion hydrobromide content is released after about 8 hours. After about 16 hours more
than about 70% ofthe bupropion hydrobromide content is released. For example, in certain embodiments more than about 80% ofthe bupropion hydrobromide content is released after
about 16 hours.

In certain embodiments an enhanced absorption formulation is provided wherein not more
than about 40% is released after about 2 hours; after about 4 hours from about 40% to about
75% is released; after about 8 hours at least about 75% is released; and after about 16 hours at least about 85% is released. For example, in at least one embodiment, the bupropion
30 hydrobromide release profile is about 33% after about 2 hours; about 59% after about 4
hours; about 91% after about 8 hours; and about 97% after about 16 hours.

Controlled Release Matrix

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In other embodiments ofthe present invention, a controlled release matrix is provided from which the kinetics of drug release from the matrix core are dependent at least in part upon the diffusion and/or erosion properties of excipients within the composition. In this embodiment controlled release matrices contain an effective amount of a bupropion hydrobromide salt and
5 at least one pharmaceutically acceptable excipient. The amount ofthe bupropion
hydrobromide salt present in the controlled release matrix can vary in an amount offrom
about 40% to about 90% by weight ofthe matrix tablet dry weight, including all values and ranges therebetween. For example, in certain embodiments bupropion hydrobromide is
present in an amount from about 60% to about 80%, and in other embodiment at about 70%
10 by weight ofthe matrix tablet dry weight. The controlled release matrix can be
multiparticulate or uniparticulate, and can be coated with at least one functional or non-functional coating, or an immediate release coating containing another drug. Functional coatings include by way of example controlled release polymeric coatings, enteric polymeric coatings, and the like. Non-functional coatings are coatings that do not affect drug release
15 but which affect other properties (e.g., they can enhance the chemical, biological, or the
physical appearance ofthe controlled release formulation). Those skilled in the
pharmaceutical art and the design ofmedicaments are well aware of controlled release
matrices conventionally used in oral pharmaceutical compositions adopted for controlled
release and means for their preparation.
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Suitable excipient materials for use in such controlled release matrices are known by those of skill in the art, and include, by way of example, release-resistant or controlled release
materials such as hydrophobic polymers, hydrophilic polymers, lipophilic materials and
mixtures thereof. Non-limiting examples of hydrophobic, or lipophilic components include
25 glyceiyl monostearate, mixtures of gycery1 monostearate and glyceryl monopalmitate
(MYVAPLEXTM, Eastman Fine Chemical Company, glycerylmonooleate, a mixture of
mono, di and tri-glycerides (ATMULTM 84S), glycerylmonolaurate, paraffin, white wax, long chain carboxylic acids, long chain carboxylic acid esters, long chain carboxylic acid alcohols,
and mixtures thereof. The long chain carboxylic acids can contain from about 6 to about 30
30 carbon atoms; in certain embodiments at least about 12 carbon atoms, and in other
embodiments from about 12 to about 22 carbon atoms. In some embodiments this carbon
chain is fully saturated and unbranched, while others contain one or more double bonds. In at least one embodiment the long chain carboxylic acids contain about 3 -carbon rings or

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hydroxyl groups. Non-limiting examples of saturated straight chain acids include n-dodecanoic acid, n-tetradecanoic acid, n-hexadecanoic acid, caproic acid, caprylic acid,
capric acid, laurie acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid, melissic acid and mixtures thereof. Also useful are unsaturated monoolefluic
5 straight chain monocarboxylic acids. Non-limiting examples ofthese include oleic acid,
gadoleic acid, erucic acid and mixtures thereof. Also useful are unsaturated (polyolefinic) straight chain monocaboxyic acids. Non-limiting examples ofthese include linoleic acid, linolenic acid, arachidonic acid, behenolic acid and mixtures thereof. Useful branched acids include, for example, diacetyl tartaric acid. Non-limiting examples of long chain carboxylic
10 acid esters include glyceryl monostearates; glyceryl monopairnitates; mixtures of glyceryl
monostearate and glyceryl monopalmitate (MYVAPLEXTM 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl
monopalmitate, glyceryl monostearate glyceryl monooleate and glyceryl monolilloleate (MYVEROLTM 18-92, Eastman Fine Chemical Company); glyceryl monolinolenate; glyceryl
15 monogadoleate; mixtures of glyceryl monopalniitate, glyceryl monostearate, glyceryl
monooleate, glyceryl monolinoleate, glyceryl monolinolenate and glyceryl monogadoleate (MYVEROLTM 18-99, Eastman Fine Chemical Company); acetylated glycerides such as
distilled acetylated monoglycerides (MYVACETTM 5-07, 7-07 and 9-45, Eastman Fine
Chemical Company); mixtures of propylene glycol m.onoesters, distilled monoglycerides,
20 sodium stearoyl lactylate and silicon dioxide (MYVATEXTM TL, Eastman Fine Chemical
Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium
stearoyl lactylate and silicon dioxide (MYVATEXTM TL, Eastman Fine Chemical Company) Sd-alphatocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures ofmono- and diglyceride esters such as ATMTJLTM (Humko Chemical
25 Division of Witco Chemical); calcium stearoyl lactylate; ethoxylated mono- and di-
glycerides; lactated mono- and di-glycerides; lactylate carboxylic acid ester of glycerol and
propylene glycol; lactylic esters oflong chain carboxylic acids; polyglycerol esters oflong
chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids;
sodium stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters
30 oflong chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate;
stearyl heptanoate; cetyl esters ofwaxes; cetearyl octanoate; CIO -C30 cholesterolilavosterol esters; sucrose long chain carboxylic acid esters; and mixtures thereof. The alcohols useful as

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excipient materials for controlled release matrices can include the hydroxyl forms of the carboxylic acids exemplified above and also cetearyl alcohol.

In addition, waxes can be useful alone or in combination with the materials listed above, as
5 excipient materials for the controlled release matrix embodiments ofthe present invention.
Non-limiting examples ofthese include white wax, paraffin, microcrystalline wax, camauba
wax, and mixtures thereof.

The lipophilic agent can be present in an amount offrom about 5% to about 90% by weight
10 ofthe controlled release matrix dosage form, including all values and ranges therebetween.
For example, in certain embodiments the lipophilic agent is present in an amount of from
about 10% to about 85%, and in other embodiments from about 30% to about 60% by weight ofthe controlled release matrix dosage form.

15 Non-limiting examples of hydrophilic polymers that can be used in certain embodiments of
the controlled release matrix dosage form include hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), carboxymethylcellulose
(CMC) or other cellulose ethers, polyoxyethylene, alginic acid, acrylic acid derivatives such
as polyacrylic acid, CARBOPOLTM, polymethacrylate polymer such as EUDRAGITfi RE,
20 RS, R, S, NE and E, acrylic acid polymer, methacrylic acid polymer, hydroyethyl methacrylic
acid (HEMA) polymer, hydroxyinethyl methacrylic acid (HMMA) polymer, polyvinyl
alcohols and mixtures thereof

The hydrophilic polymer can be present in an amount of from about 10% to about 90% by
25 weight ofthe controlled release matrix dosage form, including all values and ranges
therebetween. For example, in certain embodiments the hydrophilic polymer is present in an amount of from about 20% to about 75%, and in other embodiments from about 30% to about 60% by weight ofthe controlled release matrix dosage form.

30 In at least one embodiment, the controlled release matrix dosage form comprises
hydroxypropylmethyicellulose (I-IPMC). Non-limiting examples of hydroxypropyl methylcdlluloses that can be used include METHOCELfi B (USP type 2910), METHOCELfi
F (USP type 2906), METHOCELfi J (USP type 1828), MET1-1OCELfi K (USP type 2201),

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and METHOCELfi 310 Series, products of The Dow Chemical Company, Midland, Mich., USA. The average degree ofmethoxyl substitution in these products can range from about 1.3 to about 1.9 including all values and ranges therebetween (ofthe three positions on each unit ofthe cellulose polymer that are available for substitution) while the average degree of hydroxypropyl substitution per unit expressed in molar terms can range from about 0.13 to
about 0.82 including all values and ranges therebetween. The dosage form can comprise the different HPMC grades having different viscosities. The size of a HPMC polymer is
expressed not as molecular weight but instead in terms ofits viscosity as about a 2% solution
by weight in water. Different HPMC grades can be combined to achieve the desired viscosity
10 characteristics. For example, the at least one pharmaceutically acceptable polymer can
comprise two HPMC polymers such as for example MIETHOCELfi K3 LV (which has a viscosity of about 3 cps) and METHOCELfi K100M CR (which has a viscosity of about
100,000 cps). in addition, the polymer can comprise two hydroxypropylcellulose forms such
as KLUCELfi LF and KLTJCELfi EF. In addition, the at least one polymer can comprise a
15 mixture of a KLUCELfi and a METHOCELfi.

In at least one embodiment the controlled release matrix dosage form comprises a
polyethylene oxide (PEO). PEO is a linear polymer of unsubstituted ethylene oxide. In
certain embodiments poly(ethylene oxide) polymers having viscosity-average molecular
20 weights of about 100,000 Daltons and higher are used. Non-limiting examples of
poly(ethylene oxide)s that are commercially available include: POLYOXfi NF, grade WSR
Coagulant, molecular weight 5 million; POLYOXfi grade WSR 301, molecular weight 4
. million; POLYOXfi grade WSR 303, molecular weight 7 million; POLYOXfi grade WSR.
N-60K, molecular weight 2 million; and mixtures thereof These particular polymers are
25 products ofDow Chemical Company, Midland, Mich., USA. Other examples of
polyethylene oxides exist and can likewise be used. The required molecular weight for the
PEO can be obtained by mixing PEO of differing molecular weights that are available
commercially

30 In at least one embodiment ofthe controlled release matrix dosage form, PEO and HPMC are
combined within the same controlled release matrix. In certain embodiments, the
poly(ethylenc oxide)s have molecular weights ranging from about 2,000,000 to about
10,000,000 Da including all values and ranges therebetween. For example, in at least one

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embodiment the polyethylene oxides have molecular weights ranging from about 4,000,000 to about 7,000,000 Da. In certain embodiments the HPMC polymers have a viscosity within the range of about 4,000 centipoises to about 200,000 centipoises. For example, in at least one embodiment the HPMC polymers have a viscosity offrom about 50,000 centipoises to
about 200,000 centipoises, and in other embodiments from about 80,000 centipoises to about 120,000 centipoises. The relative amounts of PEO and HPMC within the controlled release matrix can vary within the scope ofthe invention. In at least one embodiment the
PEO:HPMC weight ratio is from about 1:3 to about 3:1 including all values and ranges therebetween. For example, in certain embodiments the PEO:HPMC weight ratio is from,
10 about 1:2 to about 2:1. As for the total amount of polymer relative to the entire matrix, this
can vary as well and can depend on the desired drug loading. In at least one embodiment the total amount ofpolymer in the matrix can constitute from about 15% to about 90% by weight ofthe matrix dosage form including all values and ranges therebetween. For example, in
certain embodiments the total amount of polymer in the matrix is from about 20% to about
15 in other embodiments from about 30% to about 60%, and in still other embodiments from about 10% to about 20% by weight ofthe matrix dosage form.

In at least one embodiment ofthe invention the controlled release matrix dosage form
comprises a hydrophobic polymer such as ethylcellulose. The viscosity of ethylcellulose can
20 be selected in order to influence ofrate the drug release, In certain embodiments the
ethylcellulose has a viscosity from about 7 to about 100 cP including all values and ranges
therebetween (when measured as a 5% solution at 25°C in an Tjbbelohde viscometer, using a

46 80:20 toluene:ethanol solvent). In certain embodiments the hydrophobic polymer can
constitute from about 10% to about 90% by weight ofthe matrix dosage form including all
25 values and ranges therebetween. For example, in at least one embodiment the hydrophobic
polymer constitutes from about 20% to about 75%, and in other embodiments from about
30% to about 60% by weight ofthe matrix dosage form.

In at least one embodiment of the invention the controlled release matrix dosage form
30 comprises at least one binder. In certain embodiments the binder is water-insoluble.
Examples of binders include hydrogenated vegetable oil, castor oil, paraffin, higher aliphatic alcohols, higher aliphatic acids, long chain fatty acids, fatty acid esters, wax-like materials
such as fatty alcohols, fatty acid esters, fatty acid glycerides, hydrogenated fats,

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hydrocarbons, normal waxes, stearic acid, stearyl alcohol, hydrophobic and hydrophilic polymers having hydrocarbon backbones, and mixtures thereof. Non-limiting examples of water-soluble polymer binders include modified starch, gelatin, polyvinylpyrrolidone,
cellulose derivatives (such as for example hydroxypropyl methylcellulose (HPMC) and
5 hydroxypropyl cellulose (HPC)), polyvinyl alcohol and mixtures thereof. In at least one
embodiment, the binder can be present in an amount of from about 0.1% to about 20% by weight ofthe matrix dosage form including all values and rangs therebetween. For example,
in certain embodiments the binder is present in an amount of from about 0.5% to about 15%,
and in other embodiments from about 2% to about 10% by weight ofthe matrix dosage form.
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In at least one embodiment ofthe invention the controlled release matrix dosage form
comprises at least one lubricant. Non-limiting examples oflubricants include stearic acid, hydrogenated vegetable oils (such as hydrogenated cottonseed oil (Sterotexfi), hydrogenated soybean oil (STEROTEXfi HM) and hydrogenated soybean oil & castor wax (STIEROTEXfi
15 K)) stearyl alcohol, leucinc, polyethylene glycol (MW 1450, suitably 4000, and higher),
magnesium stearate, glyceryl monostearate, stearic acid, glycerylbehenate, polyethylene
glycol, ethylene oxide polymers (e.g. CARBOWAXfi), sodium lauryl sulfate, magnesium
lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and
mixtures thereof. The lubricant can be present in an amount of from about 0 to about 4% by
20 weight ofthe compressed uncoated matrix including all values and ranges therebetween. For
example, in certain embodiments the lubricant is present in an amount offrom about 0% to
about 2.5 % by weight ofthe compressed, uncoated matrix.

In at least one embodiment ofthe invention the controlled release matrix dosage form
25 comprises a plasticizer. Non-limiting examples ofplasticizers include dibutyl sebacate,
diethyl phthalate, triethyl citrate, tributyl citrate, triacetin, citric acid esters such as triethyl
citrate NF XVI, tributyl citrate, dibutyl phthalate, 1,2-propylene glycol, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, acetylated monoglycerides, phthalate esters,
and mixtures thereof. In at least one embodiment, the plasticizer can be present in an amount
30 offrom about 1% to about 70% by weight of the controlled release polymer in the matrix
dosage form including all values and ranges therebetween. For example, in certain
embodiments the plasticizer is present in an amount of from about 5% to about 50%, and in

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other embodiments from about 10% to about 40% by weight ofthe controlled release
polymer in the matrix dosage form.

In at least one embodiment of the invention the controlled release matrix dosage form
5 comprises at least one diluent, non-limiting examples ofwhich include dicalcium phosphate,
calcium sulfate, lactose or sucrose or other disaccharides, cellulose, cellulose derivatives,
kaolin, mannitol, dry starch, glucose or other monosaccharides, dextrin or other
polysaccharides, sorbitol, inositol, sucralfate, calcium hydroxyl-apatite, calcium phosphates,
fatty acid salts such as magnesium stearate, and mixtures thereof. In certain embodiments the
10 diluent can be added in an amount so that the combination of the diluent and the active
substance comprises up to about 60%, and in other embodiments up to about 50%, by weight ofthe composition.

In at least one embodiment ofthe invention the controlled release matrix dosage form
15 comprises a solubilizer. The solubilizer can act to increase the instantaneous solubility ofthe
bupropion salt. The solubilizer can be selected from hydrophilic surfactants or lipophilic surfactants or mixtures thereof The surfactants can be anionid, nonionic, cationic, and zwitterionic surfactants. The hydrophilic non-ionic surfactants can be selected from the
group comprised of, but not limited to: polyethylene glycol sorbitan fatty acid esters and
20 hydrophilic transesterification products of a polyol with at least one member ofthe group
from triglycerides, vegetable oils, and hydrogenated vegetable oils such as glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide, d-a-tocopheryl polyethylene glycol 1000 succinate. The ionic surfactants can be selected from
the group comprised of, but not limited to: alkylammonium salts; fusidic acid salts; fatty acid
25 derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino
acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof, camitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts;
sodium docu.sate; acyl lactylates; mono-and di-acetylated tartaric acid esters ofmono-and di-
30 glycerides; succinylated mono-and di-glycerides; citric acid esters of mono-and di-
glycerides; and mixtures thereof. The lipophilic surfactants can be selected from the group comprised of, but not limited to: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan

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fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives ofmono-and di-glycerides; hydrophobic
trailsestenfication products of a poiyol with at least one member ofthe group from
5 glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble
vitamins/vitamin derivatives; PEG sorbitan fatty acid esters, PEG glycerol fatty acid esters, polyglycerized fatty acid, polyoxycthylene-polyoxypropylene block copolymers, sorbitan
fatty acid esters; and mixtures thereof. In at least one embodiment the solubilizer can be
selected from: PEG-20-glyceryl stearate (e.g. CAPMULfi by Abitec), PEG-40 hydrogenated
10 castor oil (e.g. CREMOPHOR RH 409 by BASF), PEG 6 corn oil (e.g. LABRAFILfi by
Gattefosse), lauryl macrogol-32 glyceride (e.g. GELUCIRE44/140 by Gattefosse) stearoyl macrogol glyceride (e.g. GELUCIRE50/1 3fi by Gattefosse), polyglyceryl- 10 mono dioleate
(e.g. CAPROLfi PEG860 by Abitec), propylene glycol oleate (e.g. LUTROLfi by BASF), Propylene glycol dioctanoate (e.g. CAPTEXfi by Abitec), Propylene glycol caprylate/caprate
15 (e.g. LAI3RAFACfi by Gattefosse), Glyceryl monooleate (e.g. PECEOLfi by Gattefrosse),
Glycerol monolinoleate (e.g. MAISINEfi by Gattefrosse), Glycerol monostearate (e.g. CAPMULfi by Abitec), PEG-20 sorbitan monolaurate (e.g. TWEEN20fi by Id), PEG-4
lauryl ether (e.g. BRIJ30fi by Id), Sucrose distearate (e.g. SUCROESTER70 by
Gattefosse), Sucrose monopalmitate (e.g. STJCROESTER158 by Gattefosse),
20 polyoxyethylene-polyoxypropylene block copolymer (e.g. LUTROLfi series BASF),
polyethylene glycol 660 hydroxystearate, (e.g. SOLUTOLfi by BASF), Sodium lauryl
sulfate, Sodium dodecyl sulphate, Dioctyl suphosuccinate, L-hydroxypropyl cellulose,
. hydroxylethylcellulose, hydroxyl propylcellu.lose, Propylene glycol alginate, sodium
taurocholate, sodium glycocholate, sodium deoxycholate, betains, polyethylene glycol (e.g.
25 CARBOWAXfi by DOW), d-a-tocopheryl polyethylene glycol 1000 succinate, (Vitamin E
TPGSfi by Eastman), and mixtures thereof. In at least one other embodiment the solubilizer
can be selected from PEG-40 hydrogenated castor oil (e.g. CREMOPHOR RH 400 by
BASF), lauryl macrogol-32 glyceride (e.g. GELUCIRE44!14fi by Gattefosse) stearoyl
macrogol glyceride (e.g. GELLICIRE 50/13fi by Gattefosse), PEG-20 sorbitan monolaurate
30 (e.g. TWEEN 209 by ICI), PEG-4 lauryl ether (e.g. BRTJ309 by Id), polyoxyethylene-
polyoxypropylene block copolymer (e.g. LUTROLfi series BASF), Sodium lauryl sulphate, Sodium dodecyl sulphate, polyethylene glycol (e.g. CARBOWAXfi by DOW), and mixtures thereof.

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In at least one embodiment ofthe invention the controlled release matrix dosage form comprises a swelling enhancer. Swelling enhancers are members of a category of excipients that swell rapidly to a large extent resulting in an increase in the size ofthe tablet. At lower concentrations, these exeipients can be used as superdisintegrants; however at concentrations above 5 % w/w these agents can function as swelling enhancers and help increase the size of
the matrix dosage form. According to certain embodiments ofthe matrix dosage forms ofthe
invention, examples ofswelling enhancers include but are not limited to: low- substituted
hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium
10 carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidorie, cross-linked
polyacrylic acid, cross-linked Amberlite resin, alginates, colloidal magnesium- aluminum

16 silicate, corn starch granules, rice starch granules, potato starch granules, pregelatinised
starch, sodium carboxymethyl starch and mixtures thereof In at least one embodiment ofthe
matrix dosage forms, the swelling enhancer is cross-linked polyvinyl pyrrolidone. The
15 content ofthe swelling enhancer can be from about 5% to about 90% by weight ofthe matrix
dosage form including all values and ranges therebetween. For example, in certain
embodiments the swelling enhancer is present in an amount of from about 10% to about 70%,
and in other embodiments from about 15% to about 50% by weight ofthe matrix dosage
form.
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In at least one embodiment ofthe invention the controlled release matrix dosage form
comprises additives for allowing water to penetrate into the core of the preparation

10 (hereinafter referred to as "hydrophilic base’) In certain embodiments, the amount of water
required to dissolve 1 g ofthe hydrophilic base is not more than about 5 ml, and in other
25 embodiments is not more than about 4 ml at the temperature of about 20°C –5°C. The higher
the solubility ofthe hydrophilic base in water, the more effective is the base in allowing
water into the core ofthe preparation. The hydrophilic base includes, alia, hydrophilic
polymers such as polyethylene glycol (PEG); (e.g. PEG400, PEG1500, PEG4000, PEG6000
and PEG20000, produced by Nippon Oils and Fats Co.) and polyvinylpyrrolidone (PVP);
30 (e.g. PYP K30, ofBASF), sugar alcohols such as Dsorbitol, xylitol, or the like, sugars such
as sucrose, anhydrous maltose, D-fructose, dextran (e.g. dextran 40), glucose or the like, surfactants such as polyoxyethylene-hydrogenated castor oil (HCO; e.g. CREMOPHORfi RH40 produced by BASF, HCO-40 and HCO-60 produced by Nikko Chemicals Co.),

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polyoxyethylene-polyoxypropylene glycol (e.g. Pluronicfi F68 produced by Asahi Denka Kogyo K.K.), polyoxyethylene-sorbitan high molecular fatty acid ester (TWEENfi; e.g. TWEENfi 80 produced by Kanto Kagaku K.K.), or the like; salts such as sodium chloride, magnesium chloride., or the like; organic acids such as citric acid, tartaric acid., or the like; amino acids such as glycine,.f3-alanine, lysine hydrochloride, or the like; and amino sugars
such as meglumine. In at least one embodiment the hydrophilic base is PEG6000, PVP, D-sorbitol, or mixtures thereof.

In another embodiment ofthe invention the controlled release matrix dosage form comprises
10 at least one disintegrant. Non-limiting examples of disintegrants for use in the matrix dosage
form include croscannellose sodium, crospovidone, alginic acid, sodium alginate,
methacrylic acid DVB, cross-linked PVP, microcrystalline cellulose, polactiuin potassium, sodium starch glycolate, starch, pregelatinized starch and mixtures thereof. In at least one embodiment the disintegrant is selected from cross-linked polyvinylpyrrolidone (e.g.
15 KOLLIDONfi CL), cross-linked sodium carboxymethylcellulose (e.g. AC-DI-SO]TTM),
starch or starch derivatives such as sodium starch glycolate (e.g. EXPLOTABfi), or combinations with starch (e.g. PRIMOJELTM), swellable ion-exchange resins, such as AMBERLITETM IRI’ 88, formaldehyde-casein (e.g. ESMA SPRENGTM), and mixtures
thereof. In at least one embodiment the disintegrant is sodium starch glycolate. The
20 disintegrant can be present in certain embodiments in an amount offrom about 0% to about
20% ofthe total weight ofthe matrix including all values and ranges therebetween.

The controlled release matrices ofthe present invention can further contain one or more pharmaceutically acceptable excipients such as granulating aids or agents, colorants,
25 flavorants, pH adjusters, anti-adherents, glidants and like excipients conventionally used in
pharmaceutical compositions.

In at least one embodiment ofthe invention comprising water swellable polymers formulated into the matrix, the release kinetics ofthe bupropion hydrobromide salt from the matrix are
30 dependent upon the relative magnitude ofthe rate ofpolymer swelling at the moving
rubbery/glassy front and the rate ofpolymer erosion at the swollen polymer/dissolution
medium front. The release kinetics for the release ofthe bupropion hydrobromide salt from
the matrix can be approximated by the following equation:

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Mt/MT==ktn

where t is time,

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Mt is the amount ofthe pharmaceutical agent which has been released at time t,
MT is the total amount ofthe pharmaceutical agent contained in the matrix,
k is a constant, and
n is the release kinetics exponent

This equation is valid so long as n remains nearly constant. When n is equal to one, the
release ofthe pharmaceutical agent from the matrix has zero -order kinetics. The amount of
10 pharmaceutical agent released is then directly proportional to the time,

10 Where the swelling process ofthe polymer chosen for the excipient is the primary process
controlling the drug release (compared to erosion of the swollen polymer, non-zero order
release kinetics can result. Generally, these release kinetics dictate a value of n approaching
15 0.5, leading to square-root Fickian-type release kinetics.

In at least one embodiment ofthe invention, polymers are selected for inclusion into the
formulation to achieve zero order kinetics. The release kinetics ofthe matrix can also be
dictated by the pharmaceutical agent itself. A drug which is highly soluble (e.g. bupropion)
20 can tend to be released faster than drugs which have low solubility. Where a drug has high
solubility, polymer swelling and erosion takes place rapidly to maintain zero order release kinetics. Ifthe swelling and erosion take place too slowly, the swelling process ofthe
polymer is the primary process controlling the drug release (since the drug will diffuse from
the swollen polymer before the polymer erodes). In this situation, non-zero order release
25 kinetics can result. As a result, the administration of a highly soluble pharmaceutical agent
requires a relatively rapidly swelling and eroding excipient. To use such a material to
produce a matrix which will last for 24 hours can require a laije matrix. To overcome this difficulty, a doughnut-shaped matrix with a hole though the middle can be used with a less rapidly swelling and eroding polymer. With such a matrix, the surface area ofthe matrix
30 increases as the matrix erodes. This exposes more polymer, resulting in more polymer
swelling and erosion as the matrix shrinks in size. This type of matrix can also be used with very highly soluble pharmaceutical agents to maintain zero order release kinetics.

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In at least one other embodiment ofthe invention, zero order drug release kinetics can be achieved by controlling the surface area ofthe matrix dosage form that is exposed to erosion. When water is allowed to diffuse into a polymer matrix composition zero order release is obtained when the release rate is governed or controlled by erosion of a constant surface area per time unit. In order to ensure that the erosion ofthe polymer matrix composition is the predominant release mechanism, it is helpful to provide a polymer matrix composition which
has properties that ensures that the diffusion rate of water into the polymer matrix
composition substantially corresponds to the dissolution rate ofthe polymer matrix
composition into the aqueous medium. Thus, by adjusting the nature and amount of
10 constituents in the polymer matrix composition a zero order release mechanism can be
achieved. The compositions employed are coated in such a manner that at least one surface is exposed to the aqueous medium and this surface has a substantially constant or controlled
surface area during erosion. In the present context controlled surface area relates to a predetermined surface area typically predicted from the shape ofthe coat ofthe unit dosage
15 system. It may have a simple uniform cylindrical shape or the cylindrical form can have one
or more tapered ends in order to decrease (or increase) the initial release period.
Accordingly, these embodiments provide a method for controlling the release of a bupropion salt into an aqueous medium by erosion of at least one surface of a pharmaceutical
composition comprising
20 (i) a matrix composition comprising (a) a polymer or a mixture of polymers, (b) a bupropion
hydrobromide salt and, optionally, (c) one or more pharmaceutically acceptable excipients,
and

(ii) a coating having at least one opening exposing at the one surface ofsaid matrix, the
coating comprising: (a) a first cellulose derivative which has thermoplastic properties and
25 which is substantially insoluble in the aqueous medium in which the composition is to be
used, and at least one of (b) a second cellulose derivative which is soluble or dispersible in
water, (c) optionally a plasticizer, or (d) a filler, the method comprising adjusting the concentration and/or the nature ofthe ingredients making up the matrix composition in such a manner that the diffusion rate ofthe aqueous medium into the matrix composition
30 corresponds to 100%+30% such as, for example 100%–25%,1.00%–20%, 100%+15% or
1000/o+10%, or 100% ofthe dissolution rate of the matrix composition so as to obtain a zero order release of at least about 60% w/w such as, for example at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at

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least about 90% w/w, at least about 95% w/w or at least about 97% to about 98% w/w ofthe bupropion hydrobromide salt from the pharmaceutical composition when subject to an in-
vitro dissolution test.

5 In at least one other embodiment ofthe invention, zero order drug release is approached
through the use of: (a) a deposit-core comprising the bupropion hydrobromide salt and having
defined, geometric form, (b) a support-platform applied to said deposit-core, and is
characterized in that the deposit-core contains, mixed with the bupropion hydrobromide salt,
a polymeric material having a high degree ofswelling on contact with water or aqueous
10 liquids, a gellable polymeric material, said polymeric materials being replaceable by a single
polymeric material having both swelling and gelling properties, and other adjuvants able to

10 provide the mixture with suitable characteristics for its compression and for its intake of

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water, said support-platform comprising a polymeric material insoluble in aqueous liquids
and partially coating said deposit-core.

These and further characteristics and advantages ofthe system according to certain
embodiments ofthe matrix dosage form will be more apparent from the description of
embodiments ofthe invention given hereinafter by way of non-limiting example. The
deposit-core can generally be obtained by compressing the mixture containing the bupropion
20 hydrobromide salt to a pressure of from about 1000 to about 4000 kg/cm2 including all
values and ranges therebetween, to thus assume a defined geometric form. Polymeric
materials having a high degree ofswelling can generally be cross-linked insoluble polymers,

40 whereas gellable polyreric materials are soluble, and can control the intake ofwater.

25 The coating platform comprises a polymeric material insoluble in water and optionally
insoluble in biodegradable biological liquids, and able to maintain its impermeability
characteristics at least until the complete transfer of the bupropion hydrobromide salt
contained in the deposit-core. It is applied to a part ofthe external deposit-core surface
chosen such as to suitably direct and quantitatively regulate the release of the bupropion
30 hydrobromide salt. In this respect, as the support-platform is impermeable to water, the
polymeric material ofthe deposit-core in certain embodiments can swell only in that portion ofthe deposit not coated with the platform.

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The support-platform can be obtained by compressing prechosen polymeric materials onto the deposit-core, by immersing the deposit-core in a solution ofsaid polymeric materials in normal organic solvents, or by spraying said solutions. Polymeric materials usable for preparing the support-platform can be chosen from the class comprising acrylates, celluloses
and derivatives such as ethylcellulose, cellulose acetate-propionate, polyethylenes and methacrylates and copolymers of acrylic acid, polyvillylalcohols and mixtures thereof This platform can have a thickness of from about 2 mm (for example, if applied by compression)
to about 10 microns (for example, if applied by spraying or immersion) including all values
and ranges therebetween, and comprises from about 10% to about 90% ofthe total surface of
10 the system including all values and ranges therebetween.

A factor in controlling the release ofthe bupropion hydrobromide salt is the intensity and
duration ofthe swelling force developed by the swellable polymeric materials contained in
the deposit-core on contact with aqueous fluids. In this respect, the energy for activating,
15 executing and regulating the release ofthe bupropion hydrobromide salt can be determined
by the swelling force developed in the deposit-core when this comes into contact with water or.with biological liquids. Said force has an intensity and duration which can vary in relation
to the type and quantity ofthe polymeric materials used in formulating the deposit, and it lies between limits having a maximum value which occurs in the case of a deposit mainly
20 containing the swellable polymer, and a minimum value which occurs in the case of a deposit
mainly containing the gellable polymer. Said swellable polymer can be present in an amount offrom about 5% to about 80% by weight including all values and ranges therebetween, and
said gellable polymer present in an amount offrom about 10% to about 90% by weight
including all values and ranges therebetween, with respect to the mixture forming the deposit-
25 core.

A further control factor is the geometry ofthe support-platform, which limits the swelling of
the deposit and directs the emission ofmaterial from it. Within the scope ofthese
embodiments it is possible to conceive many systems for the controlled release ofbupropion
30 hydrobromide, which base their operation on the swelling force and differ from each other by
the type of support-platform used.

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In at least one other embodiment ofthe invention designed to achieve zero order release of
the bupropion hydrobromide salt, the kinetics of drug release from a controlled release matrix
is governed by a combination of different polymers with different swelling characteristics.
More specifically, the bupropion hydrobromide salt is first granulated with or encapsulated in
5 a less swellable polymer, such as a gum, to form a granule. This granule is disposed in a
matrix of a more swellable, erodible polymer. The more swellable erodible polymer has a diffusion rate coefficient which is greater than the difthsion rate coefficient ofthe relatively
less swellable polymer. Averaged over the entire period of drug release, the diffusion rate for
the more swellable polymer is greater than the diffusion rate for the less swellable polymer.
10 it is this general difference in rates of diffusion between the first and second polymers which

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controls the rate of drug release and allows the system to approach zero order drug delivery
over the drug release period. In at least one embodiment, pectin and HPMC are present as
the more swellable polymers in ratios offrom about 2:7 to about 4:5 including all values and ranges therebetween, and gelatin is present as the less swellable polymer.

In at least one other embodiment ofthe invention there is provided a controlled release matrix composition comprising bupropion hydrobromide incorporated within a homogeneous matrix including effective amounts of at least two polymers having opposing wettability
characteristics, wherein at least one polymer is selected which demonstrates a stronger
20 tendency towards hydrophobicity and the other polymer(s) is selected which demonstrates a
stronger tendency towards hydrophilicity. In at least one embodiment the polymer
demonstrating a stronger tendency towards hydrophobicity is ethylcellulose (EC) whereas the polymer demonstrating a stronger tendency towards hydrophilicity is hydroxyethylcellulose (HEC) and/or hydroxypropyl methylcellulose (HPMC). The composition and device ofthe
25 present invention can be provided as a matrix and can be optionally encased in a coating
material which prevents the burst and/or food effect associated with orally ingested
medicaments and imparts gastrointestinal "stealth" characteristics. In accordance with at
least one embodiment is a method for preparing a device for the controlled release ofthe bupropion hydrobromide salt, the method comprising blending bupropion hydrobromide with
30 from about 5% to about 25% by weight of hydrophilic polymer including all values and
ranges therebetween, and from about 1% to about 25% by weight of hydrophobic polymer including all values and ranges therebetween, adding suitable pharmaceutical excipients,
surface active agents and lubricants, granulating the mixture with solvents such as isopropyl

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alcohol, drying the granular mixture, milling the dried mixture, adding from about 5% to about 70% by weight of ethylcellulose including all values and ranges therebetween, adding a lubricant and optionally a glidant and compressing the granules into matrices. The matrices
are optionally encased in a gastrointestinal encasement or a pharmaceutically acceptable film coat,

In another embodiment ofthe present invention, a swellable matrix dosage form is provided
in which the bupropion hydrobromide salt is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower
10 than its swelling rate, and that releases the bupropion hydrobromide salt primarily by
diffusion. The rate of diffusion ofthe bupropion hydrobromide salt out ofthe swellable
matrix can be slowed by increasing the drug particle size, by the choice of polymer used in
the matrix, and/or by the choice of molecular weight ofthe polymer. The swellable matrix is comprised of a relatively high molecular weight polymer that swells upon ingestion. In at
15 least one embodiment the swellable matrix swells upon ingestion to a size that is at least
twice its unswelled volume, and that promotes gastric retention during the fed mode. Upon swelling, the swellable matrix can also convert over a prolonged period oftime from a glassy
polymer to a polymer that is rubbery in consistency, or from a crystalline polymer to a
rubbery one. The penetrating fluid then causes release ofthe bupropion hydrobromide salt in
20 a gradual and prolonged manner by the process ofsolution diffusion, i.e., dissolution ofthe
bupropion hydrobromide salt in the penetrating fluid and diffusion ofthe dissolved bupropion hydrobromide salt back out ofthe swellable matrix. The swellable matrix itselfis solid prior
. to administration and, once administered, remains undissolved in (i.e., is not eroded by) the
gastric fluid for a period oftime sufficient to permit the majority ofthe bupropion
25 hydrobromide salt to be released by the solution diffusion process during the fed mode. The

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rate-limiting factor in the release ofthe bupropion hydrobromide salt from the swellable
matrix is therefore controlled diffusion ofthe bupropion hydrobromide salt from the
swllable matrix rather than erosion, dissolving or chemical decomposition of the swellable matrix.

As such, the swelling ofthe polymeric matrix can achieve at least the following objectives:
(i) renders the matrix sufficiently large to cause retention in the stomach during the fed mode; (ii) localizes the release ofthe drug to the stomach and small intestine so that the drug will

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have its full effect without colonic degradation, inactivation, or loss of bioavailability; (iii) retards the rate of diffusion ofthe drug long enough to provide multi-hour, controlled
delivery of the drug into the stomach.

5 The bupropion hydrobromide salt in the swellable matrix can be present in an effective
amount of from about 0.1% to about 99% by weight ofthe matrix including all values and ranges therebetwcen. For example, in certain embodiments bupropion hydrobromide is
present in the swellable matrix in an amount of from about 0.1% to about 90%, in other embodiments from about 5% to about 90%, in still other embodiments from about 10% to
10 about 80%, and in even still other embodiments from about 25% to about 80% by weight of
the swellable matrix.

The water-swellable polymer forming the swellable matrix in accordance with these embodiments ofthe present invention can be any polymer that is non-toxic, that swells in a
15 dimensionally unrestricted manner upon imbibition of water, and that provides for a modified
release ofthe bupropion hydrobromide salt. Non-limiting examples of polymers suitable for
use in the swellable matrix include cellulose polymers and their derivatives, such as for
example, hydroxyethylcellulose, hydroxypropylcellulose, carboxyrnethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyallcylene oxides,
20 polyethylene glycols, chitosan, poly(vinyi alcohol), xanthan gum, maleic anhydride
copolymers, polyvinyl pyrrolidone), starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly(ethyleneimine), polyurethane hydrogels, and crosslinked polyacrylic acids
and their derivatives, and mixtures thereof. Further examples include copolymers ofthe polymers listed in the preceding sentence, including block copolymers and grafted polymers.
25 Specific examples of copolymers include PLURONICfi and TECTONICfi, which are
polyethylene oxide-polypropylene oxide block copolymers.

The terms "cellulose" and"cellulosic", as used within this section regarding the swellable
matrix embodiments ofthe present invention, can denote a linear polymer of anhydroglucose.
30 Non-limiting examples of cellulosic polymers include alkyl-substituted cellulosic polymers
that ultimately dissolve in the gastrointestinal (CI) tract in a predictably delayed manner. In certain embodiments the alkyl-substituted cellulose derivatives are those substituted with
alkyl groups of 1 to 3 carbon atoms each. Non-limiting examples include methyloellulose,

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hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyimethylcellulose, carboxymethylcellulose, and mixtures thereof. In terms of
their viscosities, one class of alkyl-substituted celluloses includes those whose viscosity is
within the range of about 100 to about 110,000 centipoises as a 2% aqueous solution at 20°C.
5 Another class includes those whose viscosity is within the range of about 1,000 to about
4,000 centipoises as a 1% aqueous solution at 20°C. In certain embodiments the alkyl-substituted ceiluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. In at
least one embodiment the hydroxyethylcellulose is NATRASOLfi 250HX NF.

10 Polyallcylene oxides that can be used in certain embodiments ofthe swellable matrices
include those having the properties described above for alkyl-substituted cellulose polymers.
In at least one embodiment the polyalkylene oxide is poly(ethylene oxide), which term is
used herein to denote a linear polymer of unsubstituted ethylene oxide. In at least one embodiment the poly(ethylene oxide) polymers have molecular weights of about 4,000,000
15 and higher. For example, in certain embodiment the poly(ethylene oxide) polymers have
molecular weights within the range of about 4500,000 to about 10,000,000 including all
values and ranges therebetween, and in other embodiments have molecular weights within
the range of about 5,000,000 to about 8,000,000. In. certain embodiments the poly(ethylene oxide)s are those with a weight-average molecular weight within the range of about lx105 to
20 about 1x107, and in other embodiments within the range of about 9x105 to about 8x106.
Poly(ethylene oxide)s are often characterized by their viscosity in solution. For example, in certain embodiments the poly(ethylene oxides have a viscosity range of about 50 to about 2,000,000 centipoises for a 2% aqueous solution at 20°C. In at least one embodiment the poly(ethylene oxide) is one or more ofPOLYOXfi NF, grade WSR Coagulant, molecular
25 weight 5 million, and grade WSR 303, molecular weight 7 million. Mixtures thereof are
operable.

Polysaccharide gums, both natural and modified (semi-synthetic) can be used in the swellable matrix embodiments ofthe present invention. Non-limiting examples include dextran,
30 xanthan gum, gellan gum, welan gum, rhamsan gum, and mixtures thereof. In at least one
embodiment the polysaccharide gum is xantb.an gum.

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Crossiinked polyacrylic acids that can be used in the swellable matrices ofthe present invention include those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. In certain embodiments the
crosslinked polyacrylic acids are those with a viscosity ranging from about 4,000 to about
5 40,000 centipoises for a 1% aqueous solution at 25°C. Non -limiting examples ofsuitable
crosslinked polyacrylic acids include CA8.BOPOLfi NF grades 971P, 974P and 934P. Further examples ofsuitable crosslinked polyacrylic acids include polymers known as
WATER LOCKfi, which are starcblacrylates/acrylamide copolymers.

10 The hydrophilicity and water swellability ofthese polymers can cause the drug-containing
swellable matrices to swell in size in the gastric cavity due to ingress ofwater in order to
achieve a size that can be retained in the stomach when introduced during the fed mode.
These qualities also cause the swellable matrices to become slippery, which provides
resistance to peristalsis and further promotes their retention in the stomach. The release rate
15 of drug from the swellable matrix is primarily dependent upon the rate ofwater imbibition
and the rate at which the drug dissolves and diffuses from the swollen polymer, which in turn
is related to the drug concentration in the swellable matrix. Also, because these polymers dissolve very slowly in gastric fluid, the swellable matrix maintains its physical integrity over
at least a substantial period oftime, for example in many cases at least about 90% and in
20 certain embodiments over about 100% ofthe dosing period. The particles will then slowly
dissolve or decompose. Complete dissolution or decomposition may not occur until about 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within about 10 to about 24 hours after the dosing period.

The amount of polymer relative to the drug can vary, depending on the drug release rate
desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will typically be sufficient to retain at least about 40% ofthe drug within the swellable matrix about one hour after ingestion (or immersion in the
30 gastric fluid). In certain embodiments, the amount ofpolymer is such that at least about 50%
ofthe drug remains in the matrix about one hour after ingestion; in other embodiments at
least about 60%, and in still other embodiments at least about 80% ofthe drug remains in the swellable matrix about one hour after ingestion. In certain embodiments the drug will be

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substantially all released from the swellable matrix within about 10 hours; and in other embodiments within about 8 hours, after ingestion, and the polymeric matrix will remain substantially intact until all ofthe drug is released. In other embodiments the amount of polymer will be such that after about 2 hours no more than about 40% is released; after about
4 hours from about 40% to about 75% is released; after about 8 hours at least about 75% is
released, and after about 16 hours at least about 85% is released. The term "substantially
intact is used herein to denote a polymeric matrix in which the polymer portion substantially
retains its size and shape without deterioration due to becoming solubilized in the gastric
fluid or due to breakage into fragments or small particles.

In other exemplary embodiments the swellable matrix after about 2 hours will release no

40 more than about 40% ofthe bupropion hydrobromide, after about 4 hours from about 40% to

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about 75%, after about 8 hours at least about 75%, and after about 16 hours at least about
85% ofthe bupropion hydrobromide.

The water-swellable polymers ofthe swellable matrices can be used individually or in
combination. Certain combinations will often provide a more controlled release ofthe drug
than their components when used individually. Examples include cellulose-based polymers combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined
20 with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

The benefits of certain embodiments ofthis invention can be achieved over a wide range of
drug loadings and polymer levels, with the weight ratio of drug to polymer ranging in general from about 0.01:99.99 to about 80:20, including all values and ranges therebetween. For
25 example, in certain embodiments the drug loadings (expressed in terms ofthe weight percent
of drug relative to total of drug and polymer) are within, the range of about 15% to about 80% including all values and ranges therebetween; in other embodiments within the range of about 30% to about 80% including all values and ranges therebetween; and in still other
embodiments within the range of about 30% to about 70% including all values and ranges
30 therebetween. In at least one embodiment the drug loading is within the range of about
0.01% to about 80% including all values and ranges therebetween, and in at least one other embodiment from about 15% to about 80% including all values and ranges therebetween. In
at least one embodiment the weight ratio of bupropion hydrobromide to polymer in the

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swellable matrix is from about 15:85 to about 80:20 including all valties and ranges therebetween.

The formulations ofthe swellable matrices ofthe present invention can assume the form of
5 microparticles, tablets, or microparticles retained in capsules. In at least one embodiment the
formulation comprises microparticles consolidated into a packed mass for ingestion, even
though the packed mass will separate into individual particles after ingestion. Conventional
methods can be used for consolidating the microparticles in this maimer. For example, the microparticles can be placed in gelatin capsules known in the art as ’hard-filled’ capsules and
10 "soft-elastic" capsules. The compositions of these capsules and procedures for filling them
are known among those skilled in drug formulations and manufacture. The encapsulating Imaterialshould be highly soluble so that the particles are fTeed and rapidly dispersed in the stomach after the capsule is ingested.

15 in certain embodiments ofthe swellable matrices ofthe present invention, the formulation
contains an additional amount of bupropion hydrobromide salt or other drug applied as a
quickly dissolving coating on the outside of the microparticle or tablet. This coating is
referred to as a "loading dose’ and it is included for immediate release into the recipients
bloodstream upon ingestion ofthe formulation without first undergoing the diffusion process
20 that the remainder of the drug in the formulation must pass before it is released. The "loading
dose" can be high enough to quickly raise the blood concentration ofthe drug but not high enough to produce the transient overdosing that is characteristic ofimmediate release dosage
10 forms that are not formulated in accordance with this invention.

25 In at least one embodiment ofthe swellable matrices of the present invention, the dosage
form is a size 0 gelatin capsule containing either two or three pellets of drug-impregnated polymer. For two-pellet capsules, the pellets are cylindrically shaped, about 6,6mm or about 6.7mm in diameter (or more generally, from about 6.5mm to about 7mm in diameter
including all values and ranges therebetween) and about 9.5mm or about 10.25mm in length
30 (or more generally, from about 9mm to about 12mm in length including all values and ranges
therebetween). For three-pellet capsules, the pellets are again cylindricallyshaped, about 6.6mm in diameter and about 7mm in length. For a size 00 gelatin capsule with two pellets,
the pellets are cylindrical, about 7.5mm in diameter and about 11.25mm in length, For a size

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00 gelatin capsule with three pellets, the pellets are cylindrical, about. 7.5 mm in diameter and about 7.5mm in length. In at least one other embodiment, the dosage form is a single, elongated tablet, with dimensions of about 18mm to about 22mm in length including all
values and ranges therebetween, from about 6.5mm to about 10mm in width including all
5 values and ranges therebetween, and from about 5mm to about 7.5mm in height including all
values and ranges therebetween. In at least one other embodiment, the dosage form is a
single, elongated tablet, with dimensions of from about 18mm to about 22mm in length including all values and ranges therebetween, from about 6,5mm to about 7.8mm in width including all values and ranges therebetween, and. from about 6.2mm to about 7.5mm in
10 height including all values and ranges therebetween. In at least one embodiment the
dimensions are about 20mm in length, about 6.7mm in width, and about 6.4mm, in height.
These are merely examples; the shapes and sizes can be varied considerably.

In certain embodiments the bupropion hydrobromide-containing matrix can be made
15 according to any one ofthe methods described herein.

The particulate drug/polymer mixture or drug-impregnated swellable polymer matrix of
certain embodiments can be prepared by various conventional mixing, comminution and
fabrication techniques readily apparent to those skilled in the chemistry of drug formulations.
20 Examples ofsuch techniques include: (1) Direct compression, using appropriate punches and
dies, such as those available from Elizabeth Carbide Die Company, Inc., McKeesport, Pa.,
USA; the punches and dies are fitted to a suitable rotary tableting press, such as the SElizabeth-Hata single-sided Hata Auto Press machine, with either 15, 18 or 22 stations, and available from Elizabeth-Hata International, Inc., North Huntington, Pa., USA; (2) Injection
25 or compression molding using suitable molds fitted to a compression unit, such as those
available from Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, USA.; (3)
Granulation followed by compression; and (4) Extrusion in the form of a paste, into a mold or
to an extru.date to be cut into lengths.

30 In regards to the swellable matrices of certain embodiments of the present invention, when
microparticles are made by direct compression, the addition of lubricants can be helpful and,
in certain embodiments, helpful to promote powder flow and to prevent capping ofthe microparticle (breaking off of a portion ofthe particle) when the pressure is relieved. Non-

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Limiting examples ofsuitable lubricants include magnesium stearate (in a concentration of
from about 0.25% to about 3% by weight including all values and ranges thereb etween, and
in certain embodiments less than about 1% by weight, in the powder mix), and hydrogenated vegetable oil (in certain embodiments hydrogenated and refined triglycerides ofsteaiic and
5 palntitic acids at from about 1% to about 5% by weight including all values, and ranges
therebetween, for example in at least one embodiment at about 2% by weight). Additional excipients can be added to enhance powder flowability and reduce adherence.

Certain embodiments ofthe swellable matrices ofthe present invention can find utility when
10 administered to a subject who is in the digestive state (also referred to as the postprandial or
"fed" mode). The postprandial mode is distinguishable from the interdigestive (or "fasting’) mode by their distinct patterns of gastroduodenal motor activity, which determine the gastric retention or gastric transit time ofthe stomach contents.

15 The controlled release matrices of certain embodiments ofthe present invention can be
manufactured by methods known in the art. An example of a method ofmanufacturing controlled release matrices is melt-extrusion of a mixture containing the bupropion salt, hydrophobic polymer(s), hydrophilic polymer(s), and optionally a binder, plasticizer, and
other excipient(s) as described above. Other examples of methods ofmanufacturing
20 controlled release matrices include wet granulation, dry granulation (e.g. slugging, roller
compaction.), direct compression,, melt granulation, and rotary granulation.

Additionally, controlled release particles which can be compressed or placed in capsules can
be produced by combining the bupropion hydrobromide salt and a hydrophobic fusible
25 component and/or a. diluent, optionally with a release modiiing agent including a water
soluble fusible material or a particulate soluble or insoluble organic or inorganic material. Examples of potential hydrophobic fusible components include hydrophobic materials such
as natural or synthetic waxes or oils (e.g., hydrogenated vegetable oil, hydrogenated castor
oil, microcrystalline wax, Beeswax, carnauba wax and glyceyl monostearate). In at least one
30 embodiment the hydrophobic fusible component has a melting point from about 35°C to
about 140°C including all values and ranges therebetween. Examples ofrelease modifying agents include polyethylene glycol and particulate materials such as dicalcium phosphate and

lactose.

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In certain embodiments, controlled release matrices can be produced by mechanically working a mixture of bupropion hydrobromide salt, a hydrophobic fusible component, and optionally a release component including a water soluble fusible material or a particulate
soluble or insoluble organic or inorganic material under mixing conditions that yield aglomerates, breaking down the agglomerates to produce controlled release seeds having desired release properties; and optionally adding more carrier or diluent and repeating the mixing steps until controlled release seeds having desired release properties are obtained.
These particles also can be size separated (e.g. by sieving and encapsulated in capsules or
10 compressed into a matrix).

The amount ofthe hydrophobic fusible material used in the foregoing methods can range
from. about 10% to about 90% by weight including all values and ranges therebetween.
Mixers useful in such methods are known and include conventional high-speed mixers with
15 stainless steel interiors For example, a mixture can be processed until a bed temperature of
about 40°C or higher is realized, and the mixture achieves a cohesive granular texture
comprising desired particle sizes.

As noted ifthe mixture contains agglomerates, they can be broken down using conventional
20 methods to produce a mixture of powder and particles ofthe desired size which, can be size-
separated using a sieve, screen or mesh ofthe appropriate size. This material can be returned
to a high-speed mixer and further processed as desired until the hydrophobic fusible materials begin to soften/melt, and optionally additional hydrophobic material can be added and mixing continued until particles having a desired size range are obtained. Still further, particles
25 containing bupropion hydrobromide salt can be produced by melt processing as known in the
art and combined into apsuies or compressed into matrices.

These particles can be combined with one or more excipients such as diluents, lubricants,
binding agents, flow aids, disentegrating agents, surface acting agents, water soluble
30 materials, colorants, and the like.

In addition, the controlled release matrices can optionally be coated with one or more
functional or non-functional coatings using well-known coating methods. Examples of

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coatings can include the XL controlled release coat and the EA matrix coating described herein, which can further control the release ofthe bupropion hyd.robromide salt and/or other drug.

In at least one embodiment, the controlled release matrices can each be coated with at least
one taste-masking coating. The taste-masking coating can mask the taste ofthe bupropion hydrobromide salt in the matrices. In at least one embodiment the taste-masking coating
formulations contain polymeric ingredients. It is contemplated that other excipients
consistent with the objects ofthe present invention can also be used in the taste-masking
10 coating.

SInat least one embodiment ofthe matrix dosage form, the taste-masking coating comprises a polymer such as ethyicellulose, which can be used as a dry polymer (such as ETHOCEL)
solubilised in organic solvent prior to use, or as an aqueous dispersion. One commercially-
15 available aqueous dispersion of ethylcellulose is A.QUACOATfi. AQUACOATfi can be
prepared by dissolving the ethylceliulose in a water-immiscible organic solvent and then
emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under
vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during
20 the manufacturing phase. Thus, prior to using the same as a coating, the Aquacoat is
intimately mixed with a suitable plasticizer prior to use. Another aqueous dispersion of ethylcellulose is commercially available as SURELEA.SEfi. This product can be prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of
a polymer, plasticizer (e.g. dibutyl sebacate), and stabilizer (e.g. oleic acid) is prepared as a
25 homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous
dispersion which can be applied directly onto substrates.

In other embodiments ofthe matrix dosage form, polymethacrylate acrylic polymers can be employed as taste masking polymers. In at least one embodiment, the taste masking coating
30 is an acrylic resin lacquer used in the form of an aqueous dispersion, such as EUD1OITfi
or KOLLICOATfi. In further embodiments, the acrylic coating comprises a mixture oftwo acrylic resin lacquers ETJDRAGITfi RL and EUDRAGITfi RS, respectively. EUIJRAGITfi
RL and EUDRAGITfi RS are copolymers of acrylic and methacrylic esters with a low

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content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in EUDRAGITfi RL and 1:40 in EUDRAGITfi RS. The mean molecular weight is 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties ofthese agents. EUDRAGITfi RL/RS mixtures are insoluble in water and in digestive fluids. However,
coatings formed from the same are swellable and permeable in aqueous solutions and
digestive fluids. EUDRAGITfi RL/RS dispersions or solutions ofthe certain embodiments
can be mixed together in any desired ratio in order to ultimately obtain a taste masking
coating having a desirable drug dissolution profile. Controlled release formulations of certain
10 embodiments can be obtained, for example, from a retardant coating derived from 100%
EUDRAGITfi RL; 50% ETJDRAGITfi RL with 50% ETJDRAGITfi RS; and 10% EUDRAGITfi RL with 90% EUDRAGITfi RS.

In other embodiments ofthe matrix dosage form, the taste masking polymer can be an acrylic
15 polymer which is cationic in character based on dimethylaminoethyl mcthaciylate and neutral
methacrylic acid esters (such as EEJDRAGITfi E). The hydrophobic acrylic polymer
coatings ofthe present invention can further include a neutral copolymer based on poly (meth)acrylates, such as EUDRAGITfi NE. EUDRA.GITfi NE 30D lacquer films are
insoluble in water and digestive fluids, but permeable and swellable.
20

In other embodiments ofthe matrix dosage form, the taste masking polymer is a dispersion of poly (ethylacrylate methyl methacrylate) 2:1 (KOLLICOATfi EMM 30 D).

In other embodiments ofthe matrix dosage form, the taste masking polymer can be a
25 polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as
KOLLICOATfi SR30D.

Other taste masking polymers that can be used in the matrix dosage forms include hydroxropylce1lulose (HPC); hydroxypropylmethylcellulose (HPMC);
30 hydroxyethylcellulose; gelatin; gelatin/acacia; gelatiri/acacia/vinvylmethylether maleic
anhydride; gelatinlacacialethylenemaleic anhydride; carboxymethyl cellulose; polyvinvylalcohol; nitrocellulose; polysrinylalcoholpolyethylene glycol graft-copolymers; shellac; wax and mixtures thereof.

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The taste-masking coatings can be applied to the matrices from one or more organic or
aqueous solvent solutions or suspensions. In at least one embodiment ofthe matrix dosage forms the organic solvents that can be used to apply the taste-masking coatings include one or
5 more of acetone, lower alcohols such as ethanol, isopropanol and alcohol/water mixtures,
chlorinated hydrocarbons, and the like. Devices used to coat the matrices of certain
embodiments with a taste-masking coating include those conventionally used in
pharmaceutical processing, such as fluidized bed coating devices. The controlled release
coatings applied to the matrices can contain ingredients other than the cellulosic polymers.
10 One or more colorants, flavorants, sweeteners, can also be used in the taste-masking coating.

SInsome embodiments ofthe matrix dosage forms, a pore former can be included into the taste masking coat in order to influence the rate ofrelease of bupropion hydrobromide from
the matrix. In other embodiments, a pore former is not included in the taste masking coat.
15 The pore formers can be inorganic or organic, and may be particulate in nature and include
materials that can be dissolved, extracted or leached from the coating in the environment of
use. Upon exposure to fluids in the environment ofuse, the pore-formers can for example be
dissolved, and channels and pores are formed that fill with the environmental fluid.

20 For example, the pore-formers of certain embodiments ofthe matrix dosage forms can
comprise one or more water-soluble hydrophilic polymers in order to modify the release characteristics ofthe formulation. Examples of suitable hydrophilic polymers that can be
used as pore-formers include hydroxypropylmetihylcellulose, cellulose ethers and protein-derived materials ofthese polymers, the cellulose ethers, such as hydroxyalkylceliuloses,
25 carboxyallcylcelluloses and mixtures thereof. Also, synthetic water-soluble polymers can be
used, examples ofwhich include polyvinylpyrrolidone, cross-linked polyvinyl-pyrrolidone, polyethylene oxide, water-soluble polydextrose, saccharides and polysaccharides, such as pullulan, dextran, sucrose, glucose, fructose, mannitol, lactose, mamiose, galactose, sorbitol and mixtures thereof. In at least one embodiment, the hydrophilic polymer comprises
30 hydroxypropyl-methylcellulose.

Other non-limiting examples of pore-formers that can be used in the taste masking coat
include alkali metal salts such as lithium carbonate, sodium chloride, sodium bromide,

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potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate and mixtures thereof. The pore-forming solids can also be polymers which are soluble in the environment ofuse, such as CARBOWAXTM and CARBOPOLTM. in addition, the pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols,
5 poly(a-w)alkylenediols and mixtures thereof. Other pore-formers which can be useful in the
formulations of certain embodiments ofthe present invention include starch, modified starch,
and starch derivatives, gums, including but not limited to xanthan gum, aiginic acid, other alginates, benitoniite, veegum, agar, guar, locust bean gum, gum arable, quince psyllium, flax seed, okra gum, arabinoglactin, pectin, tragacanth, scieroglucan, dextran, amylose,
10 amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, such as
potassium polymethacrylate, carrageenan, kappa-carrageenan, lambda-carrageenan, gum
karaya, biosynthetic gum, and mixtures thereof. Other pore-formers include materials useful
for making microporous lamina in the environment of use, such as polycarbonates comprised oflinear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain,
15 microporous materials such as bisphenol, a microporous polyvinylchloride), micro-porous
polyamides, microporous mod-acrylic copolymers, microporous styrene-acrylic and its copolymers, porous polysulfones, halogenated poly(vinylidene), polychloroethers, acetal polymers, polyesters prepared by esterification of a dicairboxylic acid or anhydride with an alkylene polyol, poly(all<iylenesulfides), phenolics, polyesters, asymmetric porous polymers,
20 cross-linked olefm polymers, hydrophilic microporous hiomopolymers, copolymers or
interpolymers having a reduced bulk density, and other similar materials, poly(urethane), cross-linked chain-extended polyurethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), and mixtures thereof.

25 In general, the amount of pore-former included in the taste masking coatings of certain
embodiments ofthe matrix dosage forms can be from about 0.1% to about 80%, by weight including all values and ranges therebetween, relative to the combined weight of polymer and pore-former. The percentage of pore former as it relates to the dry weight of the taste-
masking polymer, can have an influence on the drug release properties ofthe coated matrix.
30 In at least one embodiment that uses water soluble pore formers such as
hydroxypropylmethylcellulose, a taste masking polymer: pore former dry weight ratio of
from about 10:1 to about 1:1 including all values and ranges therebetween can be present. In certain embodiments the taste masking polymer: pore former dry weight ratio is from about

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8:1 to about 1.5:1 including all values and ranges therebetween; and in other embodiments from about 6:1 to about 2:1 including all values and ranges therebetween. In at least one embodiment using ETJDRAGITfi NE30D as the taste masking polymer and a hydroxypropylmethylcellulose (approx Scps viscosity (in a 2% aqueous solution)) such as
5 METHOCELfi E5, PHARMACOATfi 606G as the water soluble pore former, a taste
masking polymer: pore former dry weight ratio of about 2:1 is present.

Colorants that can be used in the taste-masking coating of certain embodiments of the matrix dosage forms include food, drug and cosmetic colors (FD&C), drug and cosmetic colors
10 (D&C) or external drug and cosmetic colors (Ext. D&C). These colors are dyes, lakes, and
certain natural and derived colorants. Useful lakes include dyes absorbed on aluminum Shydroxide or other suitable carriers.

Flavorants that can be used in the taste-masking coating of certain embodiments ofthe matrix
15 dosage forms include natural and synthetic flavoring liquids. An illustrative list ofsuch
fiavorants includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids,
oleoresins and extracts derived from plants, leaves, flowers, fruits, sterns and combinations thereof. A non-limiting representative list ofthese includes citric oils, such as lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, grape, strawberry,
20 raspberry, cherry, plum, pineapple, apricot, or other fruit flavors. Other useful flavorants
include aldehydes and esters, such as.benzaldehyde (cherry, almond); citral, i.e., alpha-citral (lemon, lime); neral, i.e., beta-citral (lemon, lime); decanal (orange, lemon); aldehyde C-8
(citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); tolyl aldehyde
(cherry, almond); 2,6-dimethyloctanal (green fruit); 2-dodenal (citrus mandarin); and
25 mixtures thereof.

Sweeteners that can be used in the taste-masking coating of certain embodiments ofthe
matrix dosage forms include glucose (corn syrup), dextrose, invert sugar, fructose, and
mixtures thereof (when not used as a carrier); saccharin and its various salts, such as sodium
30 salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin;
Steva Rebaudiana (Stevioside); chioro derivatives or sucrose such as sucralose; and sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweeteners such as 3,6-dihydro -6-methyl-1-1- 1,2,3 -

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oxathiazin4- 1 -2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and calcium salts thereof. The sweeteners can be used alone or in any combination thereof.

The matrix taste masking coat can also include one or more pharmaceutically acceptable
5 excipients such as lubricants, emulsifiers, anti-foaming agents, plasticizers, solvents and the
like.

Lubricants can be included to help reduce friction of coated matrices during manufacturing.
The lubricants that can be used in the taste masking coat of certain embodiments ofthe
10 present invention include but are not limited to adipic acid, magnesium stearate, calcium
stearate, zinc stearate, calcium silicate, magnesium silicate, hydrogenated vegetable oils,
sodium chloride, sterotex, polyoxyethyiene, glyceryl monostearate, talc, polyethylene glycol, sodium. benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stearyl furnarate,
light mineral oil, waxy fatty acid esters such as glyceryl behenate, (e.g. COMPRITOLTM),
15 STEAR-O-WETTM, MYVATEXrM TL and mixtures thereof. In at least one embodiment, the
lubricant is selected from magnesium. stearate, talc and a mixture thereof. The lubricant can
be present in an amount offrom about 1% to about 100% by weight ofthe polymer dry
weight in the taste masking coat including all values and ranges therebetween. For example,
in certain embodiments wherein the taste masking polymer is EUDRAGITfi NE30D or
20 EUDRAGITfi NE40D together with a hydrophilic pore former, the lubricant is present in an
amount of from about 1% to about 30% by weight ofthe polymer dry weight including all
values and ranges therebetween; in other embodiments from about 2% to about 20%
including all values and ranges therebetween; and in still other embodiments at about 10% by weight ofthe matrix taste masking coat dry weight. In another embodiment where the taste
25 masking polymer is ethylceilulose (ETHOCELTM PRIM, PR45, PR20, PR1O or PR7
polymer, or a mixture thereof), the lubricant can be present in an amount offrom about 10%
to about 100% by weight ofthe matrix taste-masking coat dry weight including all values and ranges therebetween; in another embodiment from about 20% to about 80% including all
values and ranges therebetween; and in still another embodiments at about 50% by weight of
30 the matrix taste masking coat dry weight. In other embodiments, the taste masking coat does
not include a pore former.

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Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the matrix
taste masking coat to facilitate actual emulsification during manufacture of the coat, and also
to ensure emulsion stability during the shelf-life ofthe product. Emulsifying agents useful
for the matrix taste masking coat composition of certain embodiments include, but are not
5 limited to naturally occurring materials and their semi synthetic derivatives, such as the
polysaccharides, as well as glycerol esters, cellulose ethers, sorbitan esters (e.g. sorbitan monooleate or SPANTM 80), and polysorbates (e.g. TWEENTM 80). Combinations of emulsifying agents are operable. In at least one embodiment, the emulsifying agent is
TWEENTM 80. The emulsifying agent(s) can be present in an amount offrom about 0.01% to
10 about 5% by weight ofthe matrix taste masking polymer thy weight including all values and
ranges therebetween. For example, in certain embodiments the emulsifying agent is present
in an amount offrom about 0.05% to about 3% including all values and ranges therebetween;
in other embodiments from about 0.08% to about 1.5% including all values and ranges therebetween, and in still other embodiments at about 0.1% by weight ofthe matrix taste
15 masking polymer dry weight.

Anti-foaming agent(s) can be included in the matrix taste masking coat to reduce frothing or foaming during manufacture ofthe coat. Anti-foaming agents useful for the coat composition include, but are not liminted to simethicone, polyglycol, silicon oil, and mixtures thereof In
20 at least one embodiment the anti-foaming agent is Simethicone C. The anti-foaming agent
can be present in an amount of from about 0.1% to about 10% ofthe matrix taste masking
coat weight including all values and ranges therebetween. For example, in certain
embodiments the anti-foaming agent is present in an amount of from about 0.2% to about 5% including all values and ranges therebetween; in other embodiments from about 0.3% to
25 about 1% including all values and ranges therebetween, and in still other embodiments at
about 0.6% by weight ofthe matrix taste masking polymer dry weight.

Plasticizer(s) can be included in the matrix taste masking coat to provide increased flexibility
and durability during manufacturing. Plasticizers that can be used in the matrix taste masking
30 coat of certain embodiments include acetylated monoglyceridos; acetyltributyl citrate, butyl
phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalatº; ethyl phthalyl
ethyl glycolate; glycerin; propylene glycol; triacetin; tripropioin; diacetin; dibutyl phthalate;
acetyl monoglyceride; acetyltriethyl citrate, polyethylene glycols; castor oil; rape seed oil,

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olive oil, sesame oil, triethyl citrate; polyhydric alcohols, glycerol, glycerin sorbitol, acetate esters, gylcerol triaeeate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidized tallate, triisoctyl trimellitate, diethyihexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-
decyl phthalate, di-n-undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate,
dibutylphthalate, dibutyisebacate, glyceroltributyrate, and mixtures thereof. The plasticizer
can be present in an amount offrom about 1% to about 80% ofthe taste masking polymer dry
10 weight including all values and ranges therebetween. For example, in certain embodiments

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the plasticizer is present in an amount of from about 5% to about 50% including all values
and ranges therebetween, in other embodiments from about 10% to about 40% including all values and ranges therebetween, and in still other embodiments at about 20% ofthe taste
masking polymer dry weight.

In some embodiments mixtures of plasticizers are provided, e.g., a mixture of PEG 4000 and Dibutyl Sebacate (DBS). For example, in a 174 mg bupropion hydrobromide tablet,
PEG4000 is present in an amount of 1.6% by weight ofthe total formulation and DBS is
present in an amount of 0.8% by weight ofthe total formulation, in a 348 mg bupropion
20 hydrobromide tablet, PEG4000 is present in an amount of 0.9% by weight ofthe total
formulation and DBS is present in an amount of 0.4% by weight ofthe total formulation, and
in a 522 mg bupropion hydrobrQnlide tablet, PEG4000 is present in an amount of 0.9% by weight ofthe total formulation and DBS is present in an amount of 0.4% by weight ofthe
total formulation,
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The taste-masking coating can be present in an amount offrom about 1% to about 90% by weight ofthe matrix including all values and ranges therebetween, depending upon the choice ofpolymer, the ratio of polymer:pore former, and the total surface area ofthe matrix
formulation. Since a certain thickness oftaste masking coating has to be achieved in order to
30 achieve effective taste masking, the amount oftaste masking polymer coating used during
manufacture is related to the total surface area ofthe batch of uncoated matrices that requires
a coating. For example, the taste masking polymer surface area coverage can range from
about 0.5 m.g/cm2 to about 20mg/cm2 including all values and ranges therebetween. For

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example, in certain embodiments the surface area coverage ofe taste masking polymer is
from about 0.6 mg/cm2 to about I Omg/cm2 including all values and ranges therebetween,
and in other embodiments is from about 1 mg/cm2 to about 5mg/crn2 including all values and ranges therebetween. In at least one embodiment of the invention, EUDRAGITfi IE is
employed as the taste masking polymer at a surface area coverage of about 4rng/cm2,

In the absence of an accurate determination oftotal surface area of a matrix, the amount of taste masking polymer to be applied can be expressed as a percentage ofthe uncoated matrix. For example, in certain embodiments the taste-masking coating is present in an amount of from about 5% to about 60% including all values and ranges therebetween; in other embodiments from about 10% to about 40% including all values and ranges therebetween; and in still other embodiments from about 15% to about 35% by weight ofthe matrix including all values and ranges therebetween, in at least one embodiment the taste-masking coating is present in an amount of about 30% by weight ofthe matrix.

Prophetic examples of matrix tablet formulations are described below. It should be understood that these examples are intended to be exemplary and that the specific constituents, amounts thereof, and formulation methods may be varied therefrom in order to achieve different release characteristics:

In at least one embodiment, the controlled matrices comprise:
Bupropion HBr about 30.0% by weight ofthe matrix Hydroxypropylmethylcellulose E50
Hydroxypropylmethylceliulose K1 5M
Calcium phosphate dehydrate

ATMIJLTM 84S

(mono/diltri glycerides)
Magnesium stearate

about 10.0% by weight ofthe matrix
about 30.0% by weight ofthe matrix
about 9.5% by weight ofthe matrix about 20.0% by weight ofthe matrix

about 0.5% by weight ofthe matrix

Preparation of the matrix formulation can be as follows: Combine the drug, a portion of each HPMC, calcium phosphate and Atmul 84S in a planetary mixer and dry mix for 15 minutes. Add a solution ofthe remainder ofthe HPMC in water to the mixer while mixing, until a wet mass is obtained. Pass the wet material through a screen to make the resultant granules of

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uniform size (to achieve uniform drying) and dry in an oven at about 40°C for about 24
hours. Mill the dried granules through a Fitzpatrick Mill, knives forward, and collect the material in a mixer. Add the magnesium stearate and mix for about 5 minutes. The resultant mixture is tabletted on a suitable tablet press.

In at least one embodiment, the controlled release matrices comprise a deposit-core and support-platform. Preparation ofthe deposit-core can be as follows: Deposit-cores can be prepared using the following materials in the stated quantities:
Bupropion HBr
hydroxypropylmethylcellulose (METHOCELfi K I OOM-Colorcon)
mannito 1

ethylcellulose (high viscosity-BDH)
375 g magnesium stearate
5:1 ethanol-chloroform mixture

The bupropion hydrobromide is mixed intimately with the mannitol and

about 45.Og
about 35.0 g
about 10.0 g
about 3.75g
about 1.0 g
about 75,0 ml

hydroxypropylmthylcellulose in a suitable mixer. The solution of ethylcellulose in ethanol-chloroform is prepared separately, and is used for wetting the previously obtained powder mixture. The resultant homogeneous mass is forced through an 800 micron screen and then dried to obtain a granulate which is passed through a 420 micron screen. The homogeneous granulate obtained is mixed with the magnesium stearate and then compressed using concave punches of diameter 7 mm (radius of curvature 9 mm) using a pressure of about 3000 kg!cm2 to obtain cylindrical deposit-cores with convex bases.

Application ofthe support-platfonn can be as follows: The support-platform can be applied by coating one or both the convex bases ofthe deposit-core with a solution of about 15g low-permeability acrylic-methacrylic copolymer (EtJDRAGITfi RS) in methylene chloride of a quantity to make up to 100 ml. Thereafter about 0.3 ml ofsaid solution is applied to each base to be covered, taking care to protect the lateral core surface. The system is then dried with tepid air. The quantity of polymeric material deposited is sufficient to keep the structure intact during transfer.

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In at least one embodiment, the matrix formulation is a polyethylene oxide (PEO) based
tablet matrix formulation comprising:
Bupropion Hydrobromide about 50%
PEO WSR Coagulant about 15%
5 (polyethylene oxide
THOCELfi K100M about 15%
(hydroxropylmethyl cellulose)
AviceiPHiOl about 19%
(microexystalline cellulose)
10 Magnesium Stearate about 1%

SPreparationofthe PEO based tablet matrix formulation can be as follows: Excipients dry blended in an appropriate mixer and compressed ioto tablets using conventional
apparatus.
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Multiparticulates
In certain embodiments ofthe present invention, a multiparticulate system is provided which
contains multiple microparticles each containing an effective amount of bupropion hydrobromide and at least one pharmaceutically acceptable excipient. The multiparticulates
20 can be contained within a capsule, or can be compressed into a matrix or tablet, that upon
ingestion dissolves into multiple units (e.g. pellets), wherein the sub-units or pellets possess
the desired controlled release properties ofthe dosage form. The multiparticulates or the multiple unit dosage forms can be surrounded by one or more coatings. Examples ofsuch coatings include polymeric controlled release coatings, delayed release coatings, enteric
25 coatings, immediate release coatings, taste-masking coatings, extended release coatings, and
non-functional coatings.

The bupropion hydrobromide salt in the microparticles of certain embodiments can be present
in an effective amount of from about 0.1% to about 99% by weight ofthe microparticles
30 including all values and ranges therebetween. For example, in certain embodiments
bupropion hydrobromide is present in the microparticles in an amount of from about 0. 1% to about 90% including all values and ranges therebetween, in other embodiments from about
5% to about 90% including all values and ranges therebetween, in still other embodiments

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from about 10% to about 80% including all values and ranges therebetween, and in even still other embodiments from about 25% to about 80% by weight ofthe microparticle including
all values and ranges therebetween. In certain embodiments wherein the microparticles are manufactured using a spheronization process, the bupropion hydrobromide can be present in
5 the microparticles in an amount of from about 0.1% to about 60% including all values and
ranges therebetween; in other such embodiments from about 5% to about 50% including all values and ranges therebetween; and instill other such embodiments from about 10% to
about 40% by weight of the microparticle including all values and ranges therebetween. In at least one embodiment wherein the microparticles are manufactured using a spheronization
10 process, the bupropion hydrobromide is present in the microparticle in an amount of about
30% by weight ofthe microparticle.

In addition to the bupropion hydrobromide salt, the microparticles ofthe present invention
also include at least one pharmaceutically acceptable excipient. Excipients can be added to
15 facilitate in the preparation, patient acceptability and functioning ofthe dosage form as a drug
delivery system. Examples of possible excipients include spheronization aids, solubility enhancers, disintegrating agents, diluents, lubricants, binders, fillers, glidants, suspending
agents, emulsifying agents, anti-foaming agents, flavoring agents, coloring agents, chemical stabilizers, pH modifiers, and mixtures thereof. Depending on the intended main function,
20 excipients to be used in formulating compositions are subcategorized into different groups.
However, one excipient can affect the properties of a composition in a series ofways, and many excipients used in compositions can thus be described as being multifunctional.

The microparticles of certain embodiments ofthe present invention can be manufactured
25 using standard techniques known to one ofskill in the art. In certain embodiments the
microparticles can be made according to any one ofthe methods described herein. Useful microparticles include drug-layered microparticles and drug-containing microparticles.

Drug-Containing Microparticles
30 Microparticles containing drug in the core can be prepared by a number of different
procedures. For example: In a spray drying process, an aqueous solution of core material and
hot solution of polymer is atomized into hot air, the water then evaporates, and the dry solid
is separated in the form of pellets, for example by air suspension. A spray-drying process can

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produce hollow pellets when the liquid evaporates at a rate that is faster than the diffusion of the dissolved substances back into the droplet interior, or if due to capillary action the
dissolved substance migrates out with the liquid to the droplet surface, leaving behind a void. Another example is a spray congealing process, where a slurry of drug material that is
5 insoluble in a moltn mass is spray congealed to obtain discrete particles of the insoluble
materials coated with the congealed substance. A further example is r fluidized bed based granulationlpclletization process, where a dry drug is suspended in a stream of hot air to form
a constantly agitated fluidized bed. An amount of binder or granulating liquid is then
introduced in a finely dispersed form to cause pelletization.
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The drug-containing microparticles of certain embodiments ofthe present invention can also

10 be made by, for example, a spheronization process. One method ofmanufacturing the drug-
containing microparticles is the applicant’s proprietary CEFORMrM (Centrifugally Extruded
& Formed Microspheres/Microparticles) technology, which is the simultaneous use of flash
15 heat and centrifugal force, using proprietary designed equipment, to convert dry powder

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systems into microparticles of uniform size and shape. The production ofmicroparticles
containing an active drug using this CEFORIVITM technology is known. Certain embodiments
ofthe present invention deal with the use of LIQUIFLASHfi processing to spheronize
compositions containing one or more active drugs to form LIQUIFLASHfi microparticles.

With the CEFORMTM technology, the processing ofthe drug-containing microparticles of
certain embodiments ofthe present invention is carried out in a continuous fashion, whereby

IV a pre-blend of drug and excipients is fed into a spinning "microsphere head’, also termed as a
"spheronizing head". The microsphere head, which is a multi-aperture production unit, spins
25 on its axis and is heated by electrical power. The drug and excipient(s) pre-blend is fed into
the center ofthe head with an automated feeder. The material moves, via centrifugal force, to
the outer rim where the heaters, located in the rim of the head, heat the material.
Microparticles are formed when the molten material exits the head, which are then cooled by
convection as they fall to the bottom ofthe microparticle chamber. The product is then
30 collected and stored in suitable product containers. Careful selection of the types and levels
of excipient(s) control microparticle properties such as sphericity, surface morphology, and dissolution rate. One advantage ofsuch a process is that the microparticles are produced and collected from a dry feedstock without the use of any solvents.

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There are at least two approaches that can be used to produce drug-containing microparticles using the CEFORM process: (i) the encapsulation approach and (ii) the co-melt approach. In the encapsulation approach, the process is conducted below the melting point ofthe drug. Therefore, the excipients are designed to melt and entrain the drug particles on passing
through the apertures to form microparticles. The resulting microparticles contain the drug,
in its native state, essentially enveloped by or as an intimate matrix with the resolidified excipients. In the co-melt approach, the process is conducted above the melting point ofthe drug. In this case, the drug and the excipients melt or become fluid simultaneously upon
10 exposure to the heat. The molten mixture exits the head and forms microparticles, which
cool as they fall to the bottom ofthe collection bin where they are collected.

In at least one embodiment the microparticles are manufactured using the encapsulation approach. In the encapsulation approach the excipient(s) which are chosen have a lower
15 melting point than the drug (e.g. bupropion hydrobromide) with which they will be

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combined. Therefore the spheronizing process can be performed at lower temperatures, than
the melting point ofthe drug. As a result, this can reduce the risk ofpolymeric
interconversion, which can occur when using processing temperatures close to the melting
point.

In a prophetic example of certain embodiments ofthe present invention, the manufacturing
process for the microparticles can hypothetically be as follows: Spheronization aid is
screened through a 425 micron (.tm) screen. In at least one embodiment, the spheronization

W aid is distilled glyceryl monostearate (i.e. DMG-03VF). About 50% ofthe spheronization aid
25 is added to a bowl in a high shear mixer. In at least one embodiment, the bowl is a 6 litre
bowl and the high shear mixer is a Diosna P1-6 high speed mixer granulator. The active drug
is then added to the bowl ofthe mixer, and then the remainder of the spheronization aid is
added. The material is then blended in the mixer for a time from about 1 minute to about 30
minutes including all values and ranges therebetween; in certain embodiments from about 3
30 minutes to about 10 minutes; and in at least one embodiment at about 6 minutes. The mixer
motor speed is from about 50 rpm to about 2000 rpm including all values and ranges therebetweeu; in certain embodiments from about 200 rpm. to about 500 rpm; and in at least
one embodiment at about 300 rpm. The chopper motor speed is from about 50 rpm to about

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2000 rpm including all values and ranges therebetween; in certain embodiments from about 200 rpm to about 500 rpm; and in at least one embodiment at about 400 rpm. The blended material is then spheronized in a CEFORMTM spheronizing head. The spheronizing head speed is from about 5 Hz to about 60 Hz including all values and ranges therebetween; in
certain embodiments from about 10 Hz to about 30 Hz; and in at least one embodiment at
about 15 Hz, In at least one embodiment the CEFORMTM spheronizing head is a 5 inch head. The spheronizing head temperature is maintained at a temperature from about 70°C to about 130°C including all values and ranges therebetween; in certain embodiments from about 90°C
to about 110°C; and in at least one embodiment at about 100°C. The microparticles obtained
10 from the spinning process are then screened through a screen that is from about 15 0.im to
about 800tm including all values and ranges therebetween.

For microparticles manufactured using a spheronization process such as the CEFORMTM process, the microparticles include, in addition to the bupropion hydrobromide salt, at least
15 one spheronization aid. Spheronization aids can assist the drug-containing mix to form
robust durable spherical particles. Some examples ofmaterials useful as spheronization aids include, but are not limited to glyceryl monostearate, glyceryl behenate, glyceryl dibebenate, glyceryl paimitostearate, hydrogenated oils such as hydrogenated castor oil marketed under
the name CUTINATM HR, fatty acid salts such as magnesium or calcium stearate, polyols
20 such as maunitol, sorbitol, xylitol, stearic acid, palmitie acid, sodium lauryl sulfate,
polyoxyethylene ethers, esterified polyoxyethylenes such as PEG-32 distearate, PEG- 150 distearate, cetostearyl alcohol, waxes (e.g. carnauba wax, white wax, paraffin wax) and wax-
like materials. Certain thermo-plastic or themio-softening polymers can also function as spheronization aids. Some non-limiting examples ofsuch thermo-plastic or thermo-softening
25 polymers include Povidone, cellulose ethers and polyvinylalcohols. Combinations of
spheronization aids can be used. In at least one embodiment, the spheronization aid includes glyceryl monostearate (i.e. DMG-03VF). The spheronization aid can be present in an amount offrom about 0.1% to about 99% by weight ofthe microparticie including all values and
ranges therebetween. For example, in certain embodiments the spheronization aid is present
30 in an amount of from about 5% to about 90% including all values and ranges therebetween,-

in

herebetween;in
other embodiments from about 10% to about 80% including all values and ranges
therebetween; in still other embodiments from about 20% to about 70% including all values
and ranges therebetween; and in even still other embodiments from about 30% to about 60%

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by weight ofthe microparticle including all values and ranges therebetween. In at least one embodiment the spheronization aid is present in an amount of about 50% by weight ofthe microparticle. In at least one other embodiment, the microparticles include about 50% (w/w)
of bupropion hydrobromide and about 50% (w/w) ofthe spheronization aid.

In certain embodiments, each microparticle can also include at least one solubility enhancer. Solubility enhancers can be surfactants. Certain embodiments ofthe invention include a solubility enhancer that is a hydrophilic surfactant. Hydrophilic surfactants can be used to provide any ofseveral advantageous characteristics to the compositions, including: increased
10 solubility ofthe bupropion hydrobromide salt in the microparticle; improved dissolution of

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the bupropion hydrobromide salt; improved solubilization ofthe bupropion hydrobromide
salt upon dissolution; enhanced absorption and/or bioavailability ofthe bupropion
hydrobromide salt. The hydrophilic surfactant can be a single hydrophilic surfactant or a
mixture of hydrophilic surfactants, and can be ionic or non-ionic.

Likewise, various other embodiments ofthe invention include a lipophilic component, which
can be a lipophilic surfactant, including a mixture of lipophilic surfactants, a triglyceride, or a
mixture thereof. The lipophilic surfactant can provide any ofthe advantageous
characteristics listed above for hydrophilic surfactants, as well as further enhancing the
20 function ofthe surfactants. These various embodiments are described in more detail below.

As is well known in the art, the terms "hydrophilic" and "lipophilic" are relative terms. To
. function as a surfactant, a compound includes polar or charged hydrophilic moieties as well
as non-polar hydrophobic (lipophilic) moieties; i.e., a surfactant compound is amphiphilic.
25 An empirical parameter commonly used to characterize the relative hydrophilicity and

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lipophilicity ofnon-ionic amphiphilic compounds is the hydrophilic-lipophilic balance (the
"HLB" value). Surfactants with lower HLB values are more lipophilic, and have greater
solubility in oils, whereas surfactants with higher HILB values are more hydrophilic, and have greater solubility in aqueous solutions.

Using HLB values as a rough guide, hydrophilic surfactants can generally be considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or

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zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic surfactants can be compounds having an HLB value less than about 10.

It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation ofindustrial, pharmaceutical and cosmetic emulsions. For many surfactants, including several polyethoxylated surfactants, it has been reported that HLB
values can, differ by as much as about 8 HLB units, depending upon the empirical method
chosen to determine the HLB value (Schott, J. Pharm, Sciences, 79(1), 87-88 (1990)).
Likewise, for certain polypropylene oxide containing block copolymers (poloxarners,
10 available commercially as PLURONICfi surfactants), the HLB values may not accurately
reflect the true physical chemical nature ofthe compounds. Finally, commercial surfactant Sproducts are generally not pure compounds, but are often complex mixtures of compounds, and the HLB value reported for a particular compound may more accurately be characteristic
ofthe commercial product of which the compound is a major component. Different
15 commercial products having the same primary surfactant component can, and typically do,

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have different HLB values. In addition, a certain amount of lot -lot variability is expected
even for a single commercial surfactant product. Keeping these inherent difficulties in mind,
and using HLB values as a guide, one skilled in the art can readily identify surfactants having suitable hydrophilicity or lipophilicity for use in the present invention, as described herein.

Solubility enhancers can be any surfactant suitable for use in pharmaceutical compositions as known in the art. Suitable surfactants can be anionic, cationic, zwitterionic or nonionic. Refined, distilled or fractionated surfactants, purified fractions thereof, or re-esterified
fractions, are within the scope ofthe invention.

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of
suitable PEG-fatty acid esters have useful surfactant properties, as is known in the art. Polyethylene glycol (PEG) fatty acid diesters are also suitable for use as surfactants in the compositions ofthe present invention, as is known in the art. In general, mixtures of
30 surfactants are also useful in the present invention, including mixtures oftwo or more
commercial surfactant products as is known in the art (e.g. PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters).

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A large number ofsuitable surfactants of different degrees of lipophilicity or hydrophilicity can be prepared by reaction of alcohols or polyalcohols with a variety of natural and/or hydrogenated oils, as is known in the art. in certain embodiments, the oils used are castor oil
or hydrogenated or an edible vegetable oil such as corn oil, olive oil, peanut oil,
palm kernel oil, apricot kernel oil, or almond oil. Non-limiting examples of alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, pentaerythritol and mixtures thereof.

Polyglycerol esters of fatty acids as is known in the art, are also suitable surfactants for the
10 present invention. Esters ofpropylene glycol and fatty acids as is known in the art are also
suitable surfactants for use in the present invention. in general, mixtures ofsurfactants are
also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters, as is known in the art, are suitable and are
commercially available. Another class ofsuitable surfactants is the class ofmono- and
15 diglycerides, as are known. in the art. These surfactants are generally lipophilic. Sterols and
derivatives ofsterols are also suitable surfactants for use in the present invention as is known
in the art. These surfactants can be hydrophilic or lipophilic. A variety of PEG-sorbitan fatty
acid esters are known in the art and are available and suitable for use as surfactants in the
present invention. In general, these surfactants are hydrophilic, although several lipophilie
20 surfactauts ofthis class can be used. Suitable ethers of polyethylene glycol and alkyl
alcohls are known in the art and are suitable surfactants for use in the present invention.

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Esters ofsugars are known in the art and are suitable surfactants for use in the present invention. Several hydrophilic PEG-alkyl phenol surfactants are known in the art and are available, and are suitable for use in the present invention.

The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure ofthe surfactants, with hydrophilic POE and lipophilic POP moieties in well-
defmed ratios and positions, provides a wide variety ofsurfactants suitable for use in the
present invention. These surfactants are available under various trade names, including
30 SYNPERONICTM PE series (ICI); PLURONICfi series, EMKALYXTM, LUTROLTM,
SUPRONICTM MONOLANTM, PLIJRACARETM, and PLURODACTM. The generic term for these polymers is"poloxamer" (CAS 9003-11-6). These polymers have the formula: HO(C2H40)a(C3H60)b(C2H40)aH

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where "a" and ’b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.. The suitable surfactants ofthis class are known in the art.

Sorbitan esters offatty acids are suitable surfactants for use in the present invention and are
5 known in the art. Esters of lower alcohols (02 to 04) and fatty acids (08 to 018) are suitable
surfactants for use in the present invention and are known in the art. Ionic surfactants,
including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants
for use in the present invention and are known in the art. In certain embodiments, the
surfactant is an anionic surfactant such as a fatty acid salt, a bile salt, or a combination
10 thereof. In other embodiments the surfactant is a cationic surfactant such as a carnitine.
Examples ofionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuceinate, sodium cholate, sodium taurocholate; lauroyl carnitine; palmitoyl carnitine; and myristoyl carnitine.

15 ionizable surfactants, when present in their unionized (neutral, non-salt) form, are lipophilic
surfactants suitable for use in the compositions ofthe present invention, and are known in the
art. Particular examples ofsuch surfactants include free fatty acids, particularly C6-C22 fatty acids, and bile acids. More specifically, suitable unionized ionizable surfactants include the
free fatty acid and bile acid forms of any ofthe fatty acid salts and bile salts.

Derivatives of oil-soluble vitamins, such as vitamins A, D, E, K, etc., are also useful
surfactants for the compositions ofthe present invention. An example ofsuch a derivative is tocopheryl PEG-1000 succinate (TPGS).

25 In certain embodiments, surfactants or mixtures ofsurfactants that solidify at ambient room

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temperature are used. In other embodiments, surfactants or mixtures ofsurfactants that
solidify at ambient room temperature in combination with particular lipophilic components,
such as triglycerides, or with addition of appropriate additives, such as viscosity modifiers, binders, thickeners, and the like, are used.

Examples of non-ionic hydrophilic surfactants include ailcylgiucosides; ailcylmaltosides; alkyithioglucosides; lauryl macrogolglyceridcs; polyoxyethylene alkyl ethers; polyoxyethylene ailcyiphenols; polyethylene glycol fatty acids esters; polyethylene glycol

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glycerol fatty acid esters; polyoxyethylene sorbitau fatty acid esters; polyoxyethylene-polyoxypropylene block copolyrners; polyglycerol fatty acid esters; polyoxyethylene
glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols
5 with fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar
esters, sugar ethers; sucroglycerides; polyethoxylatecl fat-soluble vitamins or derivatives; and mixtures thereof.

In certain embodiments, the non-ionic hydrophilic surfactant is selected from the group
10 comprising polyoxyethylene alkylethers; polyethylene glycol fatty acids esters; polyethylene
glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene
glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils,
and mixtures thereof. The glyceride can be a monoglyceride, diglyceride, triglyceride, or a
15 mixture thereof.

In certain other embodiments, the surfactants used are non-ionic hydrophilic surfactants that
are reaction mixtures ofpolyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils or sterols. These reaction mixtures are largely composed of the
20 transesterification products ofthe reaction, along with often complex mixtures of other
reaction products. The polyol can be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof

The hydrophilic surfactant can also be, or include as a component, an ionic surfactant.
25 Examples of ionic surfactants include allcyl ammonium salts; bile acids and salts, analogues,
and derivatives thereof; ftisidic acid and derivatives thereof; fatty acid derivatives of amino
acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides,
and polypeptides; acyl lactylates; mono-,diac etylated tartaric acid esters ofmono-
,diglycerides; succinylated monoglycerides; citric acid esters ofmono-,diglycerides; alginate
30 salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and
hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfatcs; salts offatty acids; sodium docusate; camitines; and mixtures thereof.

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In certain embodiments the ionic surfactants include bile acids and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; salts of alkylsulfates; salts offatty acids; sodium docusate; acyl lactylates; mono-5,diacetylated tartaric acid esters ofmono-diglycerides; succinylated monoglycerides; citric acid esters ofmono-diglycerides; carnitines; and mixtures thereof.

Examples ofionic surfactants include lecithin, lysolecithin, phosphatidyicholine, phosphatidylethanolamine, phosphatidylglyccrol, phosphatidic acid, phosphatidylserine,
10 lysophosphatidylcholine, lysophosphatidylethanolarnine, lysophosphatidyiglycerol,
lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanoJ amine, lactylic esters of fatty acids, stearoyl-2-iactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate,
15 glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glyco deoxycholate,
glyco chenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, pairnitatc, oleate, ricinaleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl camitines, palmitoyl
20 carnitines, myristoyl carnitines, and salts and mixtures thereof.

In certain embodiments; ionic surfactants used include lecithin, lysolecithin,
phosphatidyicholine, phosphatidylcthanolamine,
lysophosphatidyicholine, PEG-phosphatidylethanolamine, lactylic esters offatty acids,
25 stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated
tartaric acid esters of mono/diglycerides, citric acid esters ofmono/diglycerides, cholate, taurocholate, glyco cholate, deoxycholate, taurodeoxycholate, glycodeoxycholate, oholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lanryl sulfate, docusate, and salts and mixtures thereof. In at least one embodiment, the ionic surfactant is selected from
30 lecithin, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters ofmono/diglycerides, taurocholate, caprylate, caprate, oleate, lauiyl sulfate, docusate, and
salts and mixtures thereof.

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Examples oflipophilic surfactants include alcohols; polyoxyethylene alkylethers; fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids
esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters;
5 polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of
mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers;
transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sueroglycerides; polyoxyethylene vegetable oils polyoxyethylene hydrogenated vegetable
10 oils; and mixtures thereof.

As with the hydrophilic surfactants, lipophilic surfactants can be reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

15 In certain embodiments, the lipophilic surfactants include one or more selected from the
group comprising fatty acids; lower alcohol fatty acid esters; polyethylene glycol glycerol
fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol
fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of
mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters;
20 polyoxyethylene-poiyoxypropylene block copolymers; polyoxyethylene vegetable oils;
polyoxyethylene hydrogenated vegetable oils; and reaction mixtures ofpolyols and fatty
acids, glycerides, vegetable oils, hydrogenated vegetable oils, sterols, and mixtures thereof.

In certain other embodiments, the lipophilic surfactants include one or more selected from the
25 group comprising lower alcohol fatty acids esters; polypropylene glycol fatty acid esters;
propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid
esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters;
polyoxyethylene vegetable oils; and mixtures thereof. Among the glycerol fatty acid esters,
the esters can be mono- or diglycerides, or mixtures of mono- and diglycerides, where the
30 fatty acid moiety is a C6 to C22 fatty acid.

Other embodiments include lipophilic surfactants which are the reaction mixture ofpolyols
and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

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Examples of polyols are polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, and mixtures thereof.

Combinations ofsolubility enhancers (i.e. surfactants) can be used. Examples ofmacrogol
fatty acid esters useful as solubility enhancers include OBLUCIREfi 50/13 and
GELUCIREfi 44/14. In at least one embodiment the solubility enhancer is GELUCIREfi
50/13. The solubility enhancer can be present in an amount of from about 0.1% to about 70°,
by weight ofthe mieroparticle including all values and ranges therebetween. For example, in certain embodiments, the solubility enhancer is present in an amount of from about 1% to
10 about 50% including all values and ranges therebetween; in other embodiments from about

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10% to about 30% including all values and ranges therebetween; in still other embodiments
from about 15% to about 25% by weight ofthe niicroparticie including all values and ranges therebetween. In at least one embodiment the solubility enhancer is present in an amount of aboj.it 20% by weight ofthe microparticle.

It is contemplated that in some embodiments, one or more other pharmaceutically acceptable excipients consistent with the objects ofthe present invention can be used in the
microparticles, such as a lubricant, a binder, a pH modifier, a filler and/or a glidant.

20 The process for manufacturing the drug-containing micropartieles of certain embodiments of
the present invention by spheronization are not limited to the CEFORIVITM technology, and
any other technology resulting in the formation ofthe microparticles consistent with the
objects ofthe present invention can also be used. For example, microparticles of certain embodiments ofthe invention can also be manufactured by extrusion/spheronization,
25 granulation or pelletization.

Extrusion/spheronization is a multi-step process used to make uniformly sized spherical particles. The technique offers the ability to incorporate high levels of active ingredients without producing excessively large particles. The main steps in the process are:
30 Dry-mixing ofingredients to achieve a homogenous powder dispersion;
Wet massing using for example a high-shear wet granulator to form rod
shaped particles of uniform diameter;
Extrusion to form rod-shaped particles of uniform diameter;

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Spheronization to round offthe rods into spherical particles;
Screening to achieve the desired narrow particle size distribution.

The mixing vessel used for dry-mixing can be of any size and shape compatible with the size ofthe formulation to be produced. For example, commercially available mixing devices such
as planetary mixers, high shear mixers, or twin cone blenders can be used. Ifrelatively small quantities offormulation are to be prepared, a simple mortar and pestle can be sufficient to
mix the ingredients. The type ofmixing vessel would be apparent to one skilled in the pharmaceutical art. The moistened mass formed by wet-massing in conventional granulation
10 equipment is extruded through a perforated mesh in order to produce cylindrical filaments.
The port ofthe meshes can determine the diameter ofthe filaments. A port ranging from
about 0.2 mm to about 3 mm including all values and ranges therebetween, can be used in
this process. In at least one embodiment utilizing this process, the port ranges from about 0,4 mm to about 2 mm including all values and ranges therebetween. The extrusion can be
15 carried out using screw, double screw, "sieve and basket" kind, "roll extruder", "ram
extruder" extruders or any other pharmaceutically acceptable means to produce cylindrical filaments. In certain embodiments utilizing this extru.sion/spheronization process, a double
screw coaxial extruder is used. The spheronization device comprises a hollow cylinder with
a horizontal rotating plate. The filaments are broken in short segments which are transformed
20 in spherical or quasi-spherical particles on the upper surface ofthe rotating plate at a velocity
ranging from about 200 rpm to about 2,000 rpm including all values and ranges
therebetween. The particles can be dried in any pharmaceutically acceptable way, such as for example by air drying in a static condition. The particles are used as they are or they are
coated to obtain granules to use in tablets, capsules, packets or other pharmaceutical
25 formulations.

A prophetic example of an exfrusionlspheronization formulation comprising bupropion hydrobromide can be as follows: In this example, the bupropion hydrobromide can be
present in an amount of from about 1% to about 80% w/w including all values and ranges
30 therebetween. In certain embodiments within this example, the bupropion hydrobromide is
present in an amount of from about % to about 50% w/w; in other embodiments from about 10% to about 30%; and in still other embodiments about 10% w/w. In this example, the filler
can be present in an amount of from about 0% to about 80% w/w including all values and

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ranges therebetween. In certain embodiments ofthis example, the filler is present in an amount offrom about lO% to about 60%; and in other embodiments at about 40% w/w. In this example, the micro crystalline cellulose can be present in an amount offrom about 10% to about 90% w/w including all values and ranges therebetween, in certain embodiments of
this example, the microcrystalline cellulose is present in an amount of from about 10% to
about 70%; and in other embodiments from about 20% to about 50% w/w. In this example,
the binder can be present in an amount offrom about 0% to about 10% w/w including all
values and ranges therebetween. In certain embodiments ofthis example, the binder is
present in an amount of from about 1% to about 8%; and in other embodiments from about
10 2% to about 4% w/w. In this example, water can be present in an amount of from about 10%
to about 80% w/w including all values and ranges therebetween. In certain embodiments of
this example, water is present in an amount offrom about 15% to about 70%; and in other embodiments from about 20% to about 50% w/w. Suitable fillers that can be used in this
example include but are not limited to calcium phosphate dibasic, tricalcium phosphate,
15 calcium carbonate, starch (such as corn, maize, potato and rice starches), modified starches
(such as carboxymethyl starch, etc.), microcrystalline cellulose, sucrose, dextrose,
maltodextrins, lactose, and fructose. Suitable lubricants that can be used in this example
include but are not limited to metal stearates (such as calcium, magnesium on zinc stearates), stearic acid, hydrogenated vegetable oils, talc, starch, light mineral oil, sodium benzoate,
20 sodium chloride, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stearyl fumaratc,
glyceryl behenate and polyethylene glycol (such as CARBOWAXTM 4000 and 6000).
Suitable antiadherents in this example include but are not limited to colloidal silicon dioxide. Suitable binders in this example include but are not limited to ethyl cellulose, a
polymethacrylate polymer, polyvinylalcohol, polyvinyl pyrrolidone, polyvinylpyrrolidone-
25 vinylacetate copolymer (e.g. KOLLIDONfi VA64) hydroxyethylcellulose, low molecular
weight hydroxypropylmethylcellulose (e.g, viscosity of about 1-50 cps at about 20°C; about 2-12 cps at about 20°C; or about 4-6 cps at about 20°C), hydroxypropyicdllulose polymethacrylates, and mixtures thereof

30 The drug-containing microparticles formed by extrusionlspheronization in this prophetic
example can be produced using cross-linked amphipliffic polymers by the following steps: (a)
the mixing of one or more cross-linked amphiphilic polymers with bupropion hydrobromide
and optionally other pharmaceutical excipients in order to obtain a uniform mixture in the

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form of dry powder to which a suitable amount ofliquid is added to obtain a pasty consistency;) the extrusion of the mixture obtained from step (a) through a perforated mesh in order to obtain cylindrical filaments having desired length and diameter; (c) the spheronization ofthe filaments in order to obtain a product in the form ofspherical multiparticulates; (d) the drying ofthe product; and (e) the optional depositing of a drug on
the surface ofthe mieroparticles. "Cross-linked amphiphilic polymer" refers in this example
to polymers showing characteristics ofswellability in the whole pH range of aqueous
solutions and also in solvents or solvent mixtures having different polarity characteristics.
The polymers can be cross-linked either physically through the interpenetration ofthe
10 macromolecular meshes, or chemically, thus showing points oflink among the
macromolecular chains. Non-limiting examples ofsuch polymers include cross-linked
polyvinyl pyrrolidone, sodium carboxymethylcellulose, sodium glycolate starch and dextrans. Optional excipients include dispersing, emulsifying, wetting agents and coloring agents. The expression "uniform mixture" in this example means that the components ofthe mixture are
15 uniformly dispersed in the formulation by a mixing process which assures the uniform
distribution of each component. A reasonable mixing time can range from about 1 to about
60 minutes including all values and ranges therebetween, using one ofthe mixing equipments conventionally used for the dry mixing ofthe powders (e.g. "V", fixed body, rotating body,
sigma mixers). The term "liquid" in this example means any liquid substance or mix
20 (solution or emulsion) of liquids ofnormal pharmaceutical use able to moisten the powder
mix, as for example water, aqueous solutions having different pH, organic solvents ofnormal pharmaceutical use (e.g. alcohols, chlorinated solvents), and oils. Among the oils and Ssurfactants which can be used in this example are: natural oils, either saturated or unsaturated (olive, peanut, soybean, corn, coconut, palm, sesame and similar oils); semisynthetic and
25 synthetic mono-, di- and triglycerides containing saturated and/or unsaturated fatty acids and
their polyhydroxyethylated derivatives (caprico-caprilic triglycerides [MYGLIOLTM,
CAPTEXTM, LABRAFACTM, LIPOTM], saturated or unsaturated polyhydroxylated
triglycerides ofvarious kind [LABRAFILTM, LABRAFACTM Hydro, GELUCIRETM]); liquid
waxes (isopropyl myristate, isopropyl-caprinate, -caprylate, -laurate, -palmitate, -stearate);
30 fatty acids esters (ethyl oleate, oleyl oleate); silicone oils; polyethylene glycols (PEG 200,
PEG 400, PEG 600, PEG 1000, and so on); polyglycolic glycerides (for example LABRASOLTM); polyglycols (propylene glycol, tetraglycol, and ethoxydiglycol (TRANSCUTOLTM), sorbitan.-esters of fatty acids (for example SPANfi, ARLACELfi,

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BRIJfi), polyoxyethylenesorbitan esters of fatty acids (for example TWEENfi, CAPMULfi, LIPOSORBfi), polypropylene oxide-polyethylene oxide (Poloxamer) copolymers,
polyethylene glycol esters (PEG)-glyceroJ. (LABRASOLfi, LABRAFILfi), PEG esters and
long chain aliphatic acids or alcohols (for example CREMOPHORfi), polyglycerid esters (PLUROLfi), saccharide, fatty acid esters (sucro-esters), and mixtures thereof. Moreover, anionic surfactants (for example sodium lauryl sulfate, sodium stearate, sodium oleate) or cationic surfactants (for example tricctol), can be used as well as lecithins, phospholipids and their semi-synthetic or synthetic derivatives. Also bupropion hydrobromide and/or excipients
can be dissolved, dispersed and/or emulsified in such liquids.

In a particular embodiment formed by an extrusionlspheronization process from. the prophetic example described above, the moistening liquid comprises an oiL1surfactant system wherein
the bupropion hydrobromide optionally emulsified with an aqueous phase is dissolved or dispersed. The amount of liquid with respect to the solid used in the preparation ofthe
15 mixture can range from about 1% to about 80% by weight including all values and ranges
therebetween. As a prophetic example ofthis embodiment, a mixture of bupropion hydrobromide and KOLLIDONM CL in a ratio equal to about 1:3 by weight is co-milled
obtaining the mixture in the form ofpowder having about 100% of granulometry lower than
about 50 microns. The mixture is moistened using a liquid demineralized water containing
20 K.OLLIDONTM 25 (polyvinyl pyrrolidone, BASF) in a solution 3% w/w. The extrusion is
carried out forcing the moistened mass through a threader having diameter ofthe holes equal
to about 1 mm. The operative parameters in this prophetic example can be as follows:

40 powder flow rate: about 4.5 kg/h; liquid flow rate: about 4.1 kg/h; torsional stress: about
27%; head temperature: about 46°C; and screw rotation velocity: about 140 rpm. The
25 extrusion filaments are then processed in a spheronizator adjusted at a velocity equal to about

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1,000 rpm for about 2 minutes. The obtained microparticles are then dried in a fluid bed for
about 2 hours to a maximum temperature equal to about 59°C. At the end of the drying the
product is discharged and is mechanically screened separating the fraction ranging from
about 0.7 mm to about 1.2 mm.

Another prophetic example of a drug-containing microparticle embodiment ofthe invention formed by an extrusionlspheronization process, uses a charged resin, the steps of which can comprise: (a) adding the charged resin, bupropion hydrobromide and other excipidnts, to a

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mixing vessel; (b) mixing the ingredients to obtain a uniform mixture; (c) adding a granulating solution - a liquid capable of wetting the dry mixture. Liquids resulting in conversion ofthe dry powder mixture into a wet granulation that supports subsequent
extrusion and spheronization (marumerization) are included. Typically, water or aqueous
5 solutions are employed. Alcohols, typically ethanol or isopropanol, can be included with the
granulating water to enhance the workability ofthe granulation. In another embodiment of
this invention, one or more ofthe components ofthe formulation is first dissolved in water
and this solution is used to produce the wet granulation. An active ingredient or an excipient which is present at very low concentration can initially be dissolved or suspended in the
10 granulating solvent to assure more uniform distribution throughout the formulation. (d)
granulating the mixture until a unifonn granulation results; (e) extruding the wet granulation through a screen to produce strands of granulation; (f) spheronizing the strands of
granulation to produce spherical muitiparticulates; and (g) collecting and drying the spherical multiparticulates. By "charged resin" is meant in this example to mean a polymer with
15 ionizable functional groups that becomes useful in the embodiment ofthis invention. This
broadly encompasses any polymer that upon ionization, is capable of producing cationic or anionic polymeric chains and which support spheronization. Typically from about 10% to
about 70% by weight ofthe spherical multiparticulate is charged resin. Non limiting
examples ofthese charged resins include sodium polystyrene sulfonate (e.g. AMBERLITE
20 IRP69’M; the chloride salt of cholestyramine resin USP (e.g. AMBERLITE IRP276TM; the
acid form ofmethacrylic acid-divinyl benzene (e.g. AMBERLITE IRP64T111; carboxypolymethylenes (e.g. CARBOPOLTM 974P and CARBQPOLTM 934P, and sodium polyacrylate (e.g. AQUAKEEPTM J550. In order for the resin to maintain the desired degree ofionization, agents which produce an acidic or basic environment during granulation and
25 spheronization can be included within the formulation. Among the groups of compounds that
can exert this effect are acids, bases, and the salts of acids and bases such as adipic acid, citric acid, fumaric acid, tartaric acid, succinic acid, sodium carbonate, sodium bicarbonate, sodium citrate, sodium acetate, sodium phosphates, potassium phosphates, ammonium phosphate, magnesium oxide, magnesium hydroxide, sodium tartrate, and lromethamine. Certain
30 compounds can be added to the granulation to provide the proper degree of hydration ofthe
charged resin, medicament and excipients. These hydrating agents include sugars such as
lactose, sucrose, mannitol, sorbitol, pentaerythritol, glucose and dextrose. Polymers such as

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polyethylene glycol as well as surfactants and other organic and inorganic salts can also be used to modulate polymer hydration.

In another prophetic example, multiparticulates containing bupropion hydrobrornide can be
5 obtained as follows:
Component Percent w/w
Bupropion HBr about 8.7
Disodium Phosphate about 7.0
Monosodium phosphate about 1.7
Sodium dodecyl sulfate about 21.7
Sodium Chloride about 17.4
Povidonc 29-32K about 8,7
AMBERLITE IRP-69 about 34.8
Butylated Hydroxyanisol about 0.0002

In this prophetic example, approximately 5.75 kg ofthe above formulation is mixed in a
planetary mixer for about 15 minutes. The butylated hydroxyanisol is dissolved in about 60
cc of ethanol and water is added to bring the final solution to a volume of about 133 cc. This
10 solution is added to the planetary mixer over about a two (2) minute period. The mixer is then
granulated with seven aliquots of about 250 cc of water added over about a fifteen minute
period. The granulation thus formed is extruded through a 1.0 -mm screen and aliquots
spheronized by marurnerization at approximately 1200 rpm for approximately 10 minutes

ID each. The spherical multiparticulates formed are then dried at about 50°C for about 24 hours.
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Another embodiment ofthis invention involves the production of drug containing
microparticles in the form of ’pearls’. Pearls can be manufactured by mixing bupropion
hydrobromide with one or more pharmaceutical excipients in molten form; the melt is forced
to pass through a nozzle which is subjected to a vibration; the pearls formed are allowed to
20 fall in a tower countercurreutwise to a gas; and the solid pearls are collected in the bottom of
the tower. In this example, the quantity of bupropion hydrobromide can vary from about 5%
to about 95% by weight including all values and ranges therebetween; and in certain
embodiments from about 40% to about 60% by weight including all values and ranges therebetween. The additives which enable the crystallization ofthe supercooled product to be

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induced in this example can be chosen from the following: fatty alcohols such as: cetyl alcohol, stearyl alcohol, fatty acids such as: stearic acid, palmitic acid, glycerol esters such as: glycerol palmitostearate, glycerol stearate (e.g. PRECIROLTM) glycerol behenate (e.g. COMPRITOLTM), hydrogenated oils such as: hydrogenated castor oil (e.g. CUTINATM BR), fatty acid salts such as: magnesium or calcium stearate, polyols such as: mannitol, sorbitol, xylitol, waxes such as: white wax, carnauba wax, paraffin wax, polyoxyctliylene glycols of
high molecular weight, and esterified polyoxyethylenes such as: PEG-32 distearate, and PEG-150 distearate. To these crystallization additives it can be desirable in this example to
add polymers which are soluble or dispersible in the melt, and which provide a controlled and
10 adjustable dissolution ofthe pearls when they are used, examples ofwhich include: cellulose
derivatives (hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyi
cellulose, ethyl cellulose, carboxymethyl cellulose), acrylic resins (e.g. EUDRAGITfi),
polyvinyl acetates (e.g. RHODOPASfi), polyalkylene (ethylene propylene), polylactic,
maleic anhydride, silicone resins, and mixtures thereof. In addition, inorganic additives can
15 be added to accelerate the solidification ofthe active substances, examples ofwhich include:
silicas, inorganic oxides such as titanium or iron oxide, phosphates, carbonates, clays, and
talc. In addition, a surface-active agent can be added to improve the dispersion ofthe active
substance in the crystallization additive, examples ofwhich include: sorbitol esters, the
polyoxyethylene polysorbates (e.g. TWEENfi), and glycols such as glycerine or propylene
20 glycol. The process for the preparation ofpearls comprise preparing a melt ofthe bupropion
hydrobromide with one or more excipients. This melt can be prepared by separately melting
the various constituents and then mixing them or by melting the mixture ofthe constituents,
. possible insoluble compounds being added at the end ofthe melting so as to obtain a
homogeneous mass. The nature ofthe constituents ofthe melt is chosen by the person skilled
25 in the art, which is considered as a function ofthe compatibility ofthe constituents, the
viscosity ofthe mixture of constituents, the nozzle diameter, the hydrophilicity ofthe active
substance, the surface tension ofthe active substance, the particle size of the insoluble
additives, the flow rate ofthe nozzle, the temperature ofthe tower, its height and, above
the size ofthe desired pearls, the proportion of bupropion hydrobromide to be included
30 therein and the desired release time ofthe active substance.

Alternative procedures other than extrusion or spheronization for manufacturing drug-containing microparticles can include wet granulation, solvent granulation and melt

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granulation. All ofthese techniques involve the addition of an inactive binder to aggregate smaller particles into larger granules. For example, wet granulation and solvent granulation involve the addition of a liquid binder which aggregates the active materials and exeipients
into granules. After granulation, the liquid can be removed by a separate drying step. Melt
5, granulation is similar to wet granulation, but uses a low melting point solid material as a
binder. The solid binder in melt granulation is melted and acts as a liquid binder thereby
aggregating the powdered active material and excipicnts into granules. The binder thereby,
can be incorporated into the granules when the granules cool.

10 Certain embodiments ofthe present invention include mieroparticles manufactured by a
process for producing granules by rotomelt granulation that comprises mixing bupropion Shydrobromide and a powdered excipient material that has a higher melting point than bupropion hydrobromide in a zone wherein both powdered materials are maintained in a
fluidized state by a rising stream of gas in an apparatus having a rapidly rotating horizontal-
15 disk located within a vertical vessel having a bottom surface; wherein said rapidly rotating
disk is located on the bottom surface ofthe vertical vessel wherein said gas is at a
temperature sufficientto cause the bupropion hydrobromide to at least partially melt thereby
causing said powdered materials to aggregate and form granules. Other embodiments ofthe
present invention include microparticles manufactured by a process for producing granules
20 by rotomelt granulation comprising mixing powdered binder material and bupropion
hydrobromide wherein the bupropion hydrobromide has a higher melting point than the
powdered binder material in a zone wherein both powdered materials are maintained in a

10 fluidized state by a rising stream of gas in an apparatus having a rapidly rotating horizontal-
disk located within a vertical vessel having a bottom surface; and wherein said rapidly
25 rotating disk is located the bottom surface ofthe vertical vessel wherein said gas is at a
temperature sufficient to cause the powdered binder material to at least partially melt thereby
causing said powdered materials to aggregate and form granules.

In rotomelt granulation, one ofthe feed powders must have a lower melting point than the
30 other powder in order to serve as a binder. The feed powders are introduced into a vertical
vessel with rotatable horizontal-disk located in the bottom ofthe vessel. The powder is maintained in fluidized state by at least one stream offiltered air being circulated from the bottom ofthe vertical vessel through one or more inlets. The rotatable horizontal disk is then

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rotated while the air supplied to fluidize the powder is maintained at a temperature sufficient to soften or melt the lower melting point powder. The temperature to which the binder must be heated to soften can be empirically determined by observing the formation of granules at various temperatures for various binders. It is presently believed that temperatures from
about 3°C to about 5°C below the melting point or melting range, including all values and
ranges therebetween, provides sufficient softening to result in granule formation. The lower melting point powder then acts as a binding agent to promote the aggregation of powder particles into granules. Suitable powders for use in rotomelt granulation have a diameter size
in the range offrom about 5 microns to about 150 microns including all values and ranges
10 therebetween; and in certain embodiments have a diameter size in the range of about 35
microns to about 80 microns. The temperature which the components will be exposed to depends on the binder employed to aggregate the powders. Generally, the melting point of
the binder is above about 30°C; and in certain embodiments is below about 100°C.

15 The powders used in these microparticles manufactured by rotomelt granulation can be
formed into granules by at least two alternative granulation mechanisms. The first
mechanism for granule formation utilizes a larger particulate binder and a smaller particulate
powder. The temperature during the rotomelt granulation is then elevated only to the point
where the external surface ofthe binder particles become tacky. As the second powdered
20 material of a smaller size is contacted with the tacky surface it forms a microlayer on the
surface ofthe binder particle. This granulation mechanism results in granules which have
size distribution similar to the original binder particles employed. Alternatively, the rotomelt
. granulation can be conducted at a temperature at which the binder acts as a cement bridging
the gaps between the unmelted particles (this is referred to as agglomeration). This
25 mechanism results in the formation of granules where the components are intermingled. For
each binder used the mechanism can be controlled primarily by the temperature at which the
rotomelt granulation is performed. Those skilled in the art will appreciate that the granules
formed can be observed by electron microscopy to determine the type of granulation process
occurring. If one particular type of granule is desired, the process conditions or starting
30 materials can be varied to produce the desired granules.

In at least one embodiment ofthe present invention, bupropion hydrobromide is melted to act
as a binding agent in the rotomelt granulation process. Examples ofsuitable excipients

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include those selected from the following: fillers, lubricants, glidants and antiadherents. Suitable fillers include but are not limited to calcium phosphate dibasic, tricalcium phosphate, calcium carbonate, starch (such as corn, maize, potato and rice starches), modified starches (such as carboxymethyl starch, etc.), microcrystalline cellulose, sucrose, dextrose,
maltodextrins, lactose, and fructose. The amount of binder added to aggregate the particles
into granules can be in the range of from about 10% w/w to about 80% w/w including all
values and ranges therebetween; and in certain embodiments is in the range of from about
30% w/w to about 70% w/w ofthe powdered materials in the rotomelt granulation. The
remaining weight percentage to provide a total of about 100% w/w can be one or more
10 suitable powdered pharmaceutical actives. Optionally the rotomelt granulation can also
contain from about 0% to about 60% w/w including all values and ranges therebetween, of Sone or more powdered excipients wherein the total weight of all the powdered materials equals about 100% w/w. The binder used in these embodiment ofthe invention can be a phannaceufically acceptable dry powder having a particle size in the range of from about 5
15 m to about 150 turn including all values and ranges therebetween; and in certain
embodiments in the range offrom about 35 m to about 80 him. Suitable binders for rotomelt granulation are low melting point powdered binders, examples ofwhich include:
polyethylene glycol 4000, polyethylene glycol 6000, stearic acid, and low melting point
waxes. Suitable low melting point waxes include but are not limited to glyceryl
20 monostearate, hydrogenated tallow, myristyl alcohol, myristic acid, stearyl alcohol,
substituted monoglycerides, substituted diglycerides, substituted triglycerides, white
beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides and combinations thereof. The binders can have a melting point of from about 30°C to about 100°C including
all values and ranges therebetween; and in certain embodiments from about 40°C to about 25.85°C.

As a prophetic example ofthese embodiments that are manufactured by a rotomelt
granulation process, about 320g of bupropion hydrobrornide aiid about 80g PEG 8000 is dry blended and poured into a Glatt 1.1 chamber set-up as a rotary granulator with a longitudinal
30 plate. Inlet air temperature is set to about 60°C and the product chamber heated to
approximately 50°C. The blend is fluidized at approximately 120m3/hr and the frictional
plate set to about 900rpm. The product chamber temperature is raised to about 60°C and then

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gradually reduced to about 20°C over a period of approximately 20 minutes, during which spheronization is achieved.

Other embodiments ofthe invention involve the formation of a microparticle that has a core
5 which includes bupropion hydrobromide and a compound which is sweet in taste and which
has a negative heat ofsolution. Examples of compounds falling into this category include mannitol and sorbitol. Sugars or artificial sweeteners to which, for example, menthol have
been added can also work as well. A binder and/or other excipient can also be disposed
within the core. The amount ofsweetening compound used can depend on a number of
10 factors including the size ofthe resulting microparticles, the size or volume ofthe resulting
tablet, the sturdiness ofthe microparticle-coated microparticulant, the speed at which the
tablet will disintegrate in the mouth, the degree ofsweetness imparted by the particular sweetener used, either in the microparticle or in the tablet, or both, the amount of drug used,
and the like. For example, particularly rugged microparticles can be less likely to break
15 during chewing and/or compression. Therefore, the amount of material provided to protect
against the release of objectionably flavored material can be lessened. In other cases a
greater relative amount of sweetening compound can be used. Generally, the amount of sweetening material used will range from greater than zero to about 80% ofthe weight ofthe resulting microparticles including all values and ranges therebetween. The sweetener and
20 bupropion hydrobromide can be combined in any number of known ways, such as for
example by wet granulation, dry granulation, agglomeration, or spray coating. For example,
the sweetener can be used as an adsorbent for the active agent. Alternatively, particles of
each can also be simply mixed together. One or more binders, or other adjuvants can also be
used in the formulation of a tablet as well. Binders in these embodiments include, for
25 example starch (for example, an amount of from about 5% to about 10% including all
values and ranges therebetween, as an aqueous paste); pregelatinized starch (for example, in
an amount of about 5% to about 10% including all values and ranges therebetween, added dry
to powder); gelatin (for example, in an amount of from about 2% to about 10% including all values and ranges therebetween, as an aqueous solution, or about 2% in starch paste);
30 polyvinylpyrrolidone (for example, in an amount of from about 2% to about 20% including
all values and ranges therebetween, in an aqueous or alcoholic solution); methylcellulose (for example, in an amount of from about 2% to about 10% including all values and ranges therebetween, as an aqueous solution); sodium carboxy methylcellulose (for example, in an

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amount of from about 2% to about 10% including all values and ranges therebetween, as an aqueous solution); ethylcellulose (for example, in an amount of froii about 5% to about 10% including all values and ranges therebetween, as an alcohol or hydroalcoholic solution); polyaerylan’iides (Polymer JR) (for example, in an amount of from about 2% to about 8%
5 including all values and ranges therebetween, as an aqueous solution); polyvinyloxoazolidone
(Deviex) (for example, in an amount of from about 5% to about 10% including all values and
ranges therebetween, as an aqueous or hydroalcoholic solution); and polyvinyl alcohols (for
example, an amount offrom about 5% to about 20% including all values and ranges
therebetween, in aqueous solutions). Other adjuvants can also be used in forming the core of
10 the microparticles ofthe present embodiments ofthe invention, non-limiting examples of
which include: calcium sulfate NF, Dibasic Calcium phosphate NF, Tribasic calcium sulfate INF,starch, calcium carbonate, microcrystalline cellulose, modified starches, lactose, sucrose and the like, STA-RX"M, AVICEL"TM, SOLKAFLOC’l’M BW40, alginic acid, EXPLOTABTM, AUTOTABTM, guar gum, kaolin. VECGUMTM, and bentonite. These adjuvants can be used
15 in up to about 20% w/w; and in certain embodiments are present in an amount of from about
3% to about 5% w/w including all values and ranges therebetween.

As a. prophetic example ofthese embodiments that have a core comprising bupropion
hydrobrorriide and a compound which is sweet in taste, bupropion hydrobromide can be
20 granulated using the following procedure: Polyvinylpyrrolidone K-30 USP (about 240.0 gm)
is dissolved into distilled water (about 1,890.0 gm) with agitation. Manrtitol powder USP
(about 11,160 gm) and bupropion hydrobrornide (about 600.0 gm) are placed in a Zanchetta 50-liter granulator/processor. After an initial two-minute dry riiix ofthe powders with the chopper on and the propeller adjusted to about 200 rpm., the polyvinylpyvolidone K-30
25 solution is slowly sprayed into the mixing powder bed using an air-driven spray system. The
total time of granulation including the time ofsolution addition is approximately eight
minutes. The granulation end-point is determined visually and by the consistency ofthe resulting material. The material is then discharged onto trays and dried at about 80°C
utilizing supplied dry air for a period of about six hours to a moisture content of not more
30 than about 0.08 percent. The dried material is then passed through a hammermill (knives
forward) equipped with a U.S. #40 (420 micron) screen.

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Other embodiments ofthis invention involve the combined granulation and coating of bupropion hydrobromide into microparticles in which the drug is at least partly located within the microparticle core but capable of immediate release. To do this, the bupropion hydrobromide and a granular disintegrant are first dry-mixed; the powder obtained is then granulated, in the presence of a mixture of excipients comprising at least one binder capable ofbinding the particles together to give grains; the grains thus formed are then coated by
spraying with a suspension comprising at least one coating agent and a membrane
disintegrant; and then the coated granules obtained are dried. The distinction between the
actual granulation and coating steps is relatively theoretical, insofar as, even though the
10 primary function ofthe binder used in the granulation step is to bind together the particles, it
nevertheless already partially coats the grains formed. Similarly, even though the primary

49 function ofthe coating agent used in the actual coating step is to complete the final coating of
each ofthe grains, it may, however, arbitrarily bind other coated grains by a mechanism of
granular agglomeration. The binder and the coating agent are chosen from the group
15 comprising cellulose polymers and acrylic polymers. However, even though the binder and
the coating agent are chosen from the same group of compounds, they nevertheless differ
from each other in their function as previously mentioned. Among the cellulose polymers
that can be advantageously chosen are ethylcellulose,
hydroxypropylcellulose (HPC), carboxymethylcellulose (CMC) and hydroxypropylmethylcel
20 hi-lose (HPMC), or mixtures thereof. Among the acrylic polymers that can be
advantageously chosen are the ammonio-methacrylate copolymer (EUDRAGITfi RL or RS),
the polyacrylate (EUDRAGITfi NE) and the methacrylic acid copolymer (EUDRAGITfi L
or S). In at least one embodiment, the binder is ofthe same nature as the coating agent. To further accelerate the release ofthe bupropion hydrobromide, the coating suspension also
25 comprises a permeabilizer which, on account ofits intrinsic solubility properties, causes
perforation ofthe membrane coating, thus allowing the bupropion hydrobromide to be
released. Non-limiting examples ofpermeabilizers include povidone and its derivatives, polyethylene glycol, silica, polyols and low-viscosity cellulose polymers. Polymers ofthe
type such as hypromeliose, whose viscosity is equal to about 6 centipoises, are used, for
30 example, as low-viscosity cellulose polymer. In at least one embodiment, the dry-mixing of
initial powder and the granulation, coating and drying steps are performed in a fluidized bed.
In this case, the initial powder mixture is first fluidized before being granulated by spraying
said powder with the excipient mixture comprising at least the binder, the grains obtained

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then being coated by spraying with the coating suspension, the coated granules formed finally being dried in the fluidized bed. In at least one embodiment, the mixture of excipients used during the granulation step and the coating suspension used during the coating step form a single mixture. In this case, the granulation step can be distinguished from the spraying step
by varying different parameters, such as the rate ofspraying of the mixture and the
atomization pressure of said mixture. Thus, only some ofthe mixture of excipients is used
during the granulation step, while the other portion can be used during the coating step.
Thus, the rate ofspraying ofthe coating suspension is higher during the granulation step than during the coating step, whereas the atomization pressure ofthe coating suspension is lower
10 during the granulation step than during the coating step. In practice, at the laboratory scale in
a fluidized-bed device, for example ofthe type such as Glatt GPCGI, during the granulation
step, the rate ofspraying ofthe coating suspension is from about 10 grams/minute to about 25 grams/minute including all values and ranges therebetween, and the atomization pressure is
from about 1 bar to about 1.8 bar including all values and ranges therebetween. During the
15 coating step, the rate of spraying ofthe coating suspension is from about 5 grams/minute to
about 15 grams/minute including all values and ranges therebetween, the atomization pressure is from about 1.5 bar to about 2.5 bar including all values and ranges therebetween.
In at least one embodiment, from about 10% to about 20% including all values and ranges therebetween, ofthe mixture of excipients is sprayed during the granulation step, the
20 remainder being sprayed during the coating step.

As a prophetic example of these embodiments that involve the combined granulation and
coating of bupropion hydrobromide into microparticles in which the drug is at least partly
located within the microparticle core but capable ofimmediate release, the microparticles can
25 be manufactured according to the following process: A granulation solution is first prepared
by dissolving about 48 g of ethylcellulose in about 273 g of ethyl alcohol, A coating
suspension is then prepared by mixing about 97 g of ethylcellulose, about 28.5 g of
polyethylene glycol 6000, about 26 g ofsodium croscarmellose, about 10 g of precipitated
silica and about 27.5 g of aspartam in about 1900 g of ethyl alcohol, until a homogeneous
30 suspension is obtained. The powder mixture consisting of about 700 grams of bupropion
hydrobrotnide and about 35 grams ofAcdisol is then fluidized. The granulation is then
started by spraying the granulation solution for about 15 to about 20 minutes at a spraying
rate of about 25 grams/minute and a suspension atomization pressure of about 0.8 bar. The

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actual coating is then performed by spraying the coating suspension for about 1 hour 30 minutes at a spraying rate of about 15 to about 20 grams/minute and a suspension spraying pressure of about 1.5 bar.

Other embodiments ofthe invention involve coating the bupropion hydrobromide material, thereby forming a drug-containing microparticle. One such process for achieving this
involves:

Blending and fluidizing a powder mix of active principle and an adjuvant in order to obtain individual grains,
10 Separately liquefying under warm conditions a lipid matrix agent comprising either an ester
ofhehenic acid and alcohol or an ester of palniitic/stearic acid and alcohol,
Coating the fluidized powder mix under warm conditions by spraying the lipid matrix agent
over the individual grains,
Lowering the temperature ofthe combined product in order to allow the lipid matrix agent to
15 solidify.

This process does not require an evaporation phase or a drying phase, since it does not
require a wet-route or solvent-route granulation step, thus making it possible to be freed from
any risk due to the presence oftoxic residues in the final product. Furthermore, it is not
20 necessary to carry out the quantitative determination ofthe traces ofsolvents, an analysis that
can be very expensive. According to the process ofthis embodiment ofthe invention, the
spraying conditions and thus the coating characteristics can be modified, in order to vary the
. release profile ofbupropion hydrobromide, by varying several parameters, the adjustment
characteristics ofwhich remain simple. Thus, the spraying air pressure can be increased in
25 order to promote the formation of a homogeneous film oflipid matrix agent around the
grains. Advantageously, the rate ofspraying ofthe lipid matrix agent can simultaneously be
decreased. In this case, the bupropion hydrobromide release profile, that is to say a
percentage of dissolution as a function ofthe time, is obtained which can be low,
corresponding to a slow release ofthe drug. Conversely, the spraying air pressure can be
30 decreased in order to promote the agglomeration ofthe grains with one another.
Advantageously, the rate ofspraying ofthe lipid matrix agent can simultaneously be
increased. In this case, a release profile ofthe grains obtained can be obtained which is high, corresponding to a rapid release of bupropion hydrobromide. In practice and according to

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the mass ofpowder employed, the value ofthe rate of spraying of the lipid matrix agent can be from two to four times higher when it is desired to promote the agglomeration ofthe grains with one another than when it is desired to promote the formation of a homogeneous film around the grains. On the other hand, the value ofthe spraying air pressure can be from
one to two times lower when it is desired to promote the agglomeration ofthe grains with one another than when it is desired to promote the formation of a homogeneous film around the
grains. According to the process for manufacturing these embodiments, it is possible, after
having determined a given drug release profile, to vary the values ofspraying air pressure and ofspraying rate throughout the coating stage, making it possible to promote the formation of
10 a homogeneous film around the grains or to promote the agglomeration ofthe grains. Once
the sequence of the duration ofthe spraying air pressure and ofthe spraying rate has been

10 determined, the coating operation can be carried Out continuously and automatically.
According to another characteristic ofthe process ofmanufacturing these embodiments, the
temperature ofthe mixture of liquefied matrix agent and ofspraying air is greater by about
15 35°C to about 60°C than the melting temperature ofthe lipid matrix agent. Likewise, the
temperature ofthe fluidization air and that ofthe powder is approximately equal to the
melting temperature ofthe lipid matrix agent, plus or minus about 10°C. Furthermore, in
order to obtain a mixture ofindividual grains, an air-operated fluidized bed device or a
turbine device can be used. Furthermore, the lipid matrix agent can be sprayed by the air
20 spray technique, that is to say liquid spraying under pressure in the presence of compressed
air. According to at least one embodiment, use i made of a powder comprising the drug and
the adjuvant. In other words, after mixing and fluidizing the combined constituents ofthe powder, the lipid matrix agent is sprayed over the individual grains obtained. In order to
avoid adhesion ofthe coated grains obtained, whether in the case where all the grains are
25 treated or whether in the case where only a portion ofthe grains is treated, a stage of
lubrication ofthe grains is inserted between the coating stage and the stage ofputting into a pharmaceutical form. Furthermore, in order to obtain greater stability ofthe pharmaceutical composition, that is to say in order to minimize modifications relating to the release ofthe bupropion hydrobromide over time, the granules or tablets obtained in certain embodiments
30 ofthis example can be subjected to a maturing stage in an oven, for at least about 8 hours, at
a temperature of from about 45°C to about 60°C; and in certain embodiments at about 55°C,

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As a prophetic example ofthese drug-containing microparticle embodiments that are formed by coating the bupropion hydrobromide material, the drug-containing microparticles can be manufactured according to the following process: A mixture of powder is prepared comprising: bupropion hydrobromide; dicalcium phosphate dehydrate; and
polyvinylpyrrolidone. Batches of granules are prepared by a process comprising the
following stages: the mixture ofpowder obtained is sieved; the said powder is mixed, heating while by means of an air-operated fluidized bed, in order to obtain individual grains; the lipid matrix agent (glyceryl behenate, e.g. COMPRITOLfi 880 ATO) is liquefied separately at
about 120°C; the lipid matrix agent is sprayed over the heated powder mixture, and, finally,
10 the temperature is lowered in order to allow the lipid matrix agent to solidify. These stages

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are carried out while varying various parameters, either in order to promote the formation of a homogeneous film around the grains or in order to promote the agglomeration ofthe grains,
in accordance with the following table:

Parameters Batch 1 Batch 2 Batch 3 Batch 4
by weight of lipid matrix
agent (COMPRITOLfi 888 ATO) 5 4 4 5
Fluidization air flow rate (m3/h) 80 110 80 80
Agglomeration
Atomization air pressure (bar) 2 1.5 1.5
Temperature ofthe powder bed (°C) 70 70 74
Spraying rate for COMPRITOLfi
(g/min)

42 40 40

Coating
Atomization air pressure (bar) 2.5 3.5 2 2
Temperature ofthe powder bed (°C) 70 66 71 70
Spraying rate for COMPRITOL
(g!min)

41 20 40 40

Another embodiment ofthe invention for coating the bupropion hydrobromide material, thereby forming a drug-containing microparticle, involves the formation of coated microcrystals that can subsequently be incorporated into a tablet. Through selection ofthe appropriate polymer the microcrystals can possess diversified features such as

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gastroresistauce atid controlled release due to the fact that the said coated or non-coated microcrystals and microgranules preserve, after having been shaped in the form of a multiparticulate tablet, their initial properties amongst which are included masking oftaste, gastroresistance and controlled release ofthe bupropion hydrobromide. In certain
5 embodiments ofthis example, the following non-limiting list ofpolymers can be selected for
coating ofthe bupropion hydrobromide in conventional fluidized based coating equipment: ethylcellulose (EC); hydroxypropylceilulose (HPC); hydroxypropylmethylcellulose (HPMC); gelatin; gelatin/acacia; gelatin/acacia/vinvylmethylether maleic anhydride;
gelatinlacacialethylenemaleic anhydride; carboxymethyl cellulose; polyvinvylalcohol;
10 cellulose acetate phthalate; nitrocellulose; shellac; wax; polymethacrylate polymers such as
EUDRAGITfi.RS; ETJDRAGITfi RL or combinations ofboth, EUDRAGITfi E and

S EUDRAGITfi NE30D; KOLLICOATTM SR30D; and mixtures thereof.

Drug-Layered Microparticles
15 The drug-layered microparticles of certain embodiments can be made by coating an inert
particle or core, such as a non-pareil sphere (e.g. sugar sphere), with the bupropion
hydrobromide salt and a polymeric binder. in certain embodiments ofthe drug-layered microparticles, the inert cores include water-insoluble materials such as cellulose spheres or silicon dioxide. In other embodiments, the inert cores include water-soluble materials such as
20 starch, salt or sugar spheres. The inert cores can have a diameter ranging from about 100
microns to about 2000 microns including all values and ranges therebetween. For example,
in certain embodiments the diameter ofthe inert cores range from about 150 microns to about 1500 microns. In at least one embodiment, the inert cores are sugar spheres NF, containing
not less than about 62.5 % and not more than about 91,5% ofsucrose including all values and
25 ranges therebetween: In at least one embodiment the inert cores have substantially consistent
bulk density, low friability, and low dust generation properties, In at least one embodiment,
the inert cores are coated with an osmotic sub-coat comprising an osmotic agent and a
polymeric binding agent. Further, the inert cores can initially be coated with a seal-coat to provide a more consistent core surface and to minimize any osmotic effects. The seal-coat
30 lyer can be applied to the core prior to the application ofthe drug, polymeric binder, and any
polymeric film layers. In at least one embodiment, the seal-coat layer does not substantially modify the release ofthe bupropion hydrobromide salt. Examples ofsuitable sealants that
can be used in the seal-coat include permeable or soluble agents such as hydroxypropyl

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methylcellulose, hydroxypropyl cellulose, ethylcellulose, a polyniethacrylate polymer, hydroxypropyl ethylcellulose, xanthan gum, and mixtures thereof. In at least one embodiment the sealant used in the seal-coat is hydroxypropyl methylcellulose. Other agents can be
added to improve the processability ofthe sealant. Examples ofsuch agents include talc,
5 colloidal silica, polyvinyl alcohoi titanium dioxide, micronised silica, fumed silica, glycerol
monostearate, magnesium trisilicate, magnesium stearate, and mixtures thereof. The seal-
coat layer can be applied from solution (e.g. aqueous) or suspension using a fluidised bed
coater (e.g. Wurster coating), or in a pan coating system. Examples ofsuch seal-coats
coatings are commercially available (e.g. OPADRYfi White Y-1-7000 and OPADRYfi
10 OY/B/28920 White).

The binding agent ofthese drug-layered embodiments is used to adhere the bupropion hydrobromide salt layer to the inert core or seal-coat ofthe core. In certain embodiments, the binding agent is water soluble, possesses sufficiently high adhesivity in order to adhere the
15 bupropion hydrobromide salt layer to the inert core, and possesses an appropriate viscosity to
provide substantial adhesion between the inert core and the bupropion hydrobromide salt. In other embodiments the binding agent is water-insoluble. In at least one embodiment the
binding agent is ethyl cellulose, a polymethacrylate polymer, polyvinylalcohol, polyvinyl
pyrrolidone, polyvinylpyrrolidone-vinylacetate copolymer (such as KOLLIDONfi VA64),
20 hydroxyethylcellulose, low molecular weight hydroxypropylmethylcellulose (e.g. viscosity of
about 1-50 cps at about 20°C; about 2-12 cps at about 20°C; or about 4-6 cps at about 20°C), hydroxypropylcellulose polymethacrylates, or mixtures thereof. For example, in certain
. embodiments the composition ofthe binder for bupropion hydrobromide is from about 1% to
about 25% w/w including all values and ranges tlierebetween; in other embodiments from
25 about 2% to about 10% w/w; and in still other embodiments from about 3% to about 5% w/w,
expressed as a percentage ofthe total weight ofthe core.

Solvents can be used to apply the bupropion hydrobromide salt to the inert core, examples of
which include lower alcohols such as ethanol, isopropanol and alcohol/water mixtures,
30 acetone and chlorinated hydrocarbons.

The drug-layered microparticles can be prepared by forming a suspension or solution ofthe
binder and the bupropion hydrobromide salt and then layering the suspension or solution on

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to the inert or sub-coated core using any of the layering techniques known in the art, such as fluidized bed coating or pan coating. This can be affected in a single coating or the process
can be carried out in multiple layers, optionally with intervening drying/evaporation steps.
This process can be conducted so as to produce microparticles containing a desired amount of
5 bupropion hydrobromide salt and achieve the desired dosage and release thereof upon in-vivo
administration.

In certain embodiments, the drug-layered microparticles can be manufactured using for
example, the procedure in the following hypothetical experiment: Bupropion hydrobromide
10 (about 2.8 kg) and hydroxypropyl methylcellulose (METHOCELfi ES) (about 0.40 kg) is
dissolved in a mixture ofwater and isopropyl alcohol. The active drug solution can then be Ssprayedonto sugar spheres 30/35 (about 1.06 kg) in a fluidized bed processor with a Wurster insert. The active core microparticles can then be dried in a fluidized bed processor until the
loss on drying is blow about 1%. The bupropion microparticles can then be passed through
15 a 16 mesh screen and a 30 mesh screen and microparticles can be collected that are smaller
than 16 mesh and larger than 30 mesh.

Microparticle Taste-Masking Coatings
The microparticles ofthe present invention can each be coated with at least one taste-masking
20 coating. The taste-masking coating can mask the taste of the active drug in the
microparticles. In at least one embodiment the taste-masking coating formulations contain polymeric ingredients. It is contemplated that other excipients consistent with the objects of
the present invention can also be used in the taste-masking coating.

25 In at least one embodiment, the taste-masking coating comprises a polymer such as
ethylcellulose, which can be used as a dry polymer (e.g. ETHOCELfi) solubilised in organic solvent prior to use, or as an aqueous dispersion. One commercially-available aqueous dispersion of ethylcellulose is AQUACOATfi. AQUACOATfi can be prepared by
dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the
30 same in water in the presence of a surfactant and a stabilizer. After homogenization to
generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, the AQUACOATfi is intimately mixed

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with a suitable plasticizer prior to use. Another aqueous dispersion of ethylcellulose is commercially available as SURELEASEfi. This product can be prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (e.g. dibutyl sebacate), and stabilizer (e.g. oleic acid) is prepared as a
homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

In other embodiments, polymethacryl ate acrylic polymers can be employed as taste masking polymers. In at least one embodiment, the taste masking coating is an acrylic resin lacquer
10 used in the form of an aqueous dispersion (e.g. EUDRAGITfi or KOLLICOATfi). In further
embodiments, the acrylic coating comprises a mixture oftwo acrylic resin lacquers (e.g. EUDRAGITfi RL and EUDRAGITfi RS, respectively).

EUIDRAGITfi RL and EUDRAGITfi RS are copolymers of acrylic and methacrylic esters
15 with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to
the remaining neutral(meth)acrylic esters being 1:20 in EUDRAGITfi RL and 1:40 in EUDRAGITfi RS. The mean molecular weight is 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties ofthese agents. EUDRAGITfi RL/RS mixtures are insoluble in water and in digestive fluids. However,
20 coatings formed from the same are swellable and permeable in aqueous solutions and
digestive fluids. EUDRAGITfi RL/RS dispersions or solutions of certain embodiments can
be mixed together in any desired ratio in order to ultimately obtain a taste masking coating
. having a desirable drug dissolution profile. In certain embodiments formulations can be
obtained, for example, from a coating derived from 100% EUDRAGITfi RL; 50%
25 EIJDRAGITfi RL with 50% EUDRAGITfi RS; and 10% EUDRAGITfi RL with 90%
EIJDRAGITfi RS.

In other embodiments, the taste masking polymer can be an acrylic polymer which is cationic
in character based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters
30 (e.g. EUDRAGITfi E). The hydrophobic acrylic polymer coatings ofthe present invention
can further include a neutral copolymer based on poly (methacrylates, such as EUDRAGITfi NE. EUDRAGITfi NE 30D lacquer films are insoluble in water and digestive fluids, but permeable and swellable.

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In other embodiments, the taste masking polymer is a dispersion of poly (ethylacrylate,
methyl methacrylate) 2:1 (KOLLICOATfi EMM 30 D, BASF)

5 In other embodiments, the taste masking polymer can be a polyvinyl acetate stabilized with
polyvinylpyrrolidone and sodium lauryl sulfate such as KOLLICOATfi SR30D (BASF).

Other taste masking polymers include hydroxypropylcellulose (HPC); hydroxypropylmethyicellulose (HPMC); hydroxyethylcellulose; gelatin; gelatin/acacia;
10 gelatirilacacia!vinvylmethylether maleic anhydride; gelatin/acacia/ethylenemaleic anhydride;
carboxymethyl cellulose; polyvinvylalcohol; nitrocellulose; polyvinylalcohol-polyethylene
glycol graft-copolymers; shellac; wax and mixtures thereof.

The taste-masking coatings can be applied to the microparticles from one or more organic or
15 aqueous solvent solutions or suspensions. In at least one embodiment the organic solvents
that can be used to apply the taste-masking coatings include one or more of acetone, lower alcohols such as ethanol, isopropanol and. alcohol/water mixtures, chlorinated hydrocarbons,
and the like. Devices used to coat the microparticles ofthe invention with a taste-masking coating include those conventionally used in pharmaceutical processing, such as fluidized bed
20 coating devices. The coatings applied to the microparticles can contain ingredients other than
the functional polymers. One or more colorants, flavorants, sweeteners, can also be used in
the tate-masking coating.

in some embodiments a pore former can be included into the taste masking coat in order to
25 influence the rate ofrelease of bupropion hydrobromide from the microparticle. In other
embodiments, a pore former is not included in the taste masking coat. The pore formers can
be inorganic or organic, and include materials such as particulate materials that can be
dissolved, extracted or leached from the coating in the environment of use. Upon exposure to fluids in the environment of use, the pore-formers can for example be dissolved, and channels
30 and pores are formed that fill with the environmental fluid.

For example, the pore-formers of certain embodiments can comprise one or more water-
soluble hydrophilic polymers in order to modify the release characteristics ofthe formulation.

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Examples ofsuitable hydrophilic polymers used as pore-formers include hydroxypropylmetihylcellulose, cellulose ethers and protein-derived materials ofthese polymers, the cellulose ethers, such as hydroxyalkylcelluloses and carboxyalkylcelluloses.
Also, synthetic water-soluble polymers can be used, examples of which include polyvinylpyrrolidone, cross-linked polyvinyl-pyrrolidone, polyethylene oxide, water-soluble polydextrose, saccharides and polysaccharides, such as pullulan, dextran, sucrose, glucose, fructose, mannitol, lactose, mannose, galactose, sorbitol and mixtures thereof. In at least one embodiment, the hydrophilic polymer comprises hydroxypropyl-methylcellulose.

10 Other non-limiting examples ofpore-formers that can be used in certain embodiments
containing a taste masking coat include alkali metal salts such as lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate,
sodium acetate, sodium citrate and mixtures thereof. The pore-forming solids can also be polymers which are soluble in the environment of use, such as CARBOWAXTM, and
15 CARBOPOLTM. In addition, the pore-formers embrace diols, polyols, polyhydric alcohols,
polyalllene glycols, polyglycols, poly(a-w)alkylenediols and mixtures thereof. Other pore-formers which can be useful in the formulations of certain embodiments ofthe present
invention include starch, modified starch, and starch, derivatives, gums, including but not
limited to xanthan gum, alginic acid, other alginates, benitoniite, veeguni, agar, guar, locust
20 bean guru, gum arabic, quince psyllium, flax seed, okra gum, arabinoglactin, pectin,
tragacanth, seleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpynolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambdacarrageenan, gum karaya, biosynthetic gum, and mixtures thereof. Other pore-formers include materials useful for making microporous lamina in the
25 environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in
which carbonate groups reoccur in the polymer chain, microporous materials such as
bisphenol, a microporous poly(vinylchloride), micro-porous polyamides, microporous modacrylic copolymers, microporous styrene-acrylic and its copolymers, porous
polysulfones, halogenated poly(vinylidene), polychioroethers, acetal polymers, polyesters
30 prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol,
poly(alkylenesulfides), phenolics, polyesters, asymmetric porous polymers, cross-linked olefin polymers, hydrophilic microporous hiomopolymers, copolymers or interpolymers having a reduced bulk density, and other similar materials, polyurethane), cross-linked

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chain-extended poly(urethane), poly(imides), poly(benzimidazoies), collodion, regenerated proteins, semi-solid cross-linked poly(viriylpyrrolidone), and mixtures thereof.

In general, the amount of pore-former included in the taste masking coatings of certain embodiments ofthe present invention can be from about 0.1% to about 80%, by weight including all values and ranges therebetwecn relative to the combined weight of polymer and pore-former. The percentage of pore former as it relates to the dry weight ofthe taste-
masking polymer, can have an influence on the drug release properties ofthe coated microparticle. In at least one embodiment that uses water soluble pore formers such as
10 hydroxypropylmethylcellulose, a taste masking polymer: pore former dry weight ratio of
from about 10:1 to about 1:1 including all values and ranges therebetween, can be present. In certain embodiments the taste masking polymer: pore former dry weight ratio is from about
8:1 to about 1.5:1; and in other embodiments from about 6:1 to about 2:1 In at least one embodiment using EUDRAGITfi NE30D as the taste masking polymer and a
15 hydroxypropylnietbylcellulose (approx Scps viscosity (in a 2% aqueous solution)) such as
METHOCELfi E5, Pharmacoat 606G as the water soluble pore former, a taste masking
polymer: pore former dry weight ratio of about 2:1 is present.

Colorants that can be used in the taste-masking coating include food, drug and cosmetic
20 colors FD&C), drug and cosmetic colors (D&C) or external drug and cosmetic colors (Ext.
D&C). These colors are dyes, lakes, and certain natural and derived colorants. Useful lakes include dyes absorbed on aluminum hydroxide or other suitable carriers.

Flavorants that can be used in the taste-masking coating include natural and synthetic
25 flavoring liquids. An illustrative list ofsuch flavorants includes volatile oils, synthetic flavor
oils, flavoring aromatics, oils, liquids, oleoresins and extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list ofthese includes citric oils, such as lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot,
30 or other fruit flavors. Other useful flavorants include aldehydes and esters, such as
beuzaidehyde (cherry, almond); citral, i.e., alpha-citral (lemon, lime); neral, i.e., beta-citral (lemon, lime); decanal (orange, lemon); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus

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fruits); aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyloctanal (green fruit); 2-dodenal (citrus mandarin); and mixtures thereof.

Sweeteners that can be used in the taste-masking coating include glucose (corn syrup),
dextrose, invert sugar, fructose, and mixtures thereof(when not used as a carrier); saccharin
and its various salts, such as sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Steva Rebaudiana (Stevioside; chioro derivatives
or sucrose such as sucralose; and sugar alcohols such as sorbitol, mamiitol, xylitol, and the
like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweeteners
10 such as 3,6-dihydro-6-methyl- 1-1-1,2,3-oxathiazin-4- 1 -2,2-dioxide, particularly the
potassium salt (acesulfame-K, and sodium and calcium salts thereof. The sweeteners can be used alone or in any combination thereof.

The microparticle taste masking coat can also include one or more pharmaceutically
15 acceptable excipients such as lubricants, emulsifiers, anti-foaming agents, plasticizers,
solvents and the like.

Lubricants can be included to help reduce friction of coated micropartieles during
manufacturing. The lubricants that can be used in the taste masking coat ofthe present
20 invention include but are not limited to adipic acid, magnesium stearate, calcium stearate,
zinc stearate, calcium silicate, magnesium silicate, hydrogenated vegetable oils, sodium
chloride, sterotex, polyoxyethylne, glyceryl inonostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stearyl fumarate, light
mineral oil, waxy fatty acid esters such as glyceryl behenate, (i.e. COMPRITOLTM), STEAR-
25 OWETTM, MYVATEXFM TL and mixtures thereof. In at least one embodiment, the
lubricant is selected from magnesium stearate, talc and a mixture thereof. Combinations of
these lubricants are operable. The lubricant can each be present in an amount offrom about
1% to about 100% by weight ofthe polymer dry weight in the taste masking coat including
all values and ranges therebetween. For example, in certain embodiments wherein the taste
30 masking polymer is EUDRAGITfi NE30D or EIJDRAGITfi NE40D together with a
hydrophilic pore former, the lubricant is present in an amount of from about 1% to about 30%
by weight ofthe polymer dry weight; in other embodiments from about 2% to about 20%;
and in still other embodiments at about 10% by weight of the microparticle taste masking

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coat dry weight. In another embodiment where the taste masking polymer is ethylcellulo.se (ETHOCELTM PR100, PR45, PR20, PR10 or PR7 polymer, or a mixture thereof), the lubricant can be present in an amount of from about 10% to about 100% by weight ofthe microparticle taste masking coat dry weight; in another embodiment from about 20% to about 80%; and in still another embodiments at about 50% by weight ofthe microparticle ’taste
masking coat dry weight. In other embodiments, the taste masking coat does not include a
pore former.

Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the
10 microparticle taste masking coat to facilitate actual emulsification during manufacture ofthe
coat, and also to ensure emulsion stability during the shelf-life ofthe product. Emulsifying agents useful for the microparticle taste masking coat composition of certain embodiments include, but are not limited to naturally occurring materials and their semi synthetic
derivatives, such as the polysaccharides, as well as glycerol esters, cellulose ethers, sorbitan
15 esters (e.g. sorbitan monooleate or SPANrM 80), and polysorbates (e.g. TWEENTM 80).
Combinations of emulsifying agents are operable. In at least one embodiment, the
emulsifying agent is TWEENTM 80. The emulsifying agent(s) can be present in an amount of from about 0.01% to about 5% by weight ofthe microparticle taste masking polymer dry
weight including all values and ranges therebetween. For example, in certain embodiments
20 the emulsifying agent is present in an amount offrom about 0.05% to about 3%; in other
embodiments from about 0.08% to about 1.5%, and in still other embodiments at about 0.1%
by weight ofthe microparticle taste masking polymer dry weight.

Anti-foaming agent(s) can be included in the microparticle taste masking coat to reduce
25 frothing or foaming during manufacture ofthe coat. Anti-foaming agents useful for the coat
composition include, but are not liminted to simethicone, polyglycol, silicon oil, and mixtures thereof. in at least one embodiment the anti-foaming agent is Simethicone C. The anti-
foaming agent can be present in an amount of from about 0.1% to about 10% of the microparticle taste masking coat weight including all values and ranges therebetween: For
30 example, in certain embodiments the anti-foaming agent is present in an amount of from
about 0.2% to about 5%; in other embodiments from about 0.3% to about 1%, and in still
other embodiments at about 0.6% by weight ofthe microparticle taste masking polymer dry weight.

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coat dry weight. In another embodiment where the taste masking polymer is ethylcellulose (ETHOCELTM?R100, PR45, PR20, PR1O or PR7 polymer, or a mixture thereof), the
lubricant can be present in an amount of from about 10% to about 100% by weight ofthe microparticle taste masking coat dry weight; in another embodiment from about 20% to about
5 80%; and in still another embodiments at about 50% by weight ofthe microparticle taste
masking coat dry weight. In other embodiments, the taste masking coat does not include a
pore former.

Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the
10 microparticle taste masking coat to facilitate actual emulsification during manufacture ofthe
coat, and also to ensure emulsion stability during the shelf-life ofthe prod:uct. Emulsiiing agents useful for the microparticle taste masking coat composition of certain embodiments include, but are not, limited to naturally occurring materials and their semi synthetic
derivatives, such as the polysaccharides, as well as glycerol esters, cellulose ethers, sorbitan
15 esters (e.g. sorbitan monooleate or SP.ANTM 80), and polysorbates (e.g. TWEENrM 80).
Combinations of emulsifying agents are operable. In at least one embodiment, the
emulsifying agent is TWEENTM 80. The emulsifying agent(s) can be present in an amount of from about 0.0 1% to about 5% by.weight ofthe microparticle taste masking polymer dry
weight including all values and ranges therebetween. For example, in certain embodiments
20 the emulsifying agent is present in an amount offrom about 0.05% to about 3%; in other
embodiments from about 0.08% to about 1,5%, and in still other embodiments at about 0.1%
by weight ofthe microparticle taste masking polymer dry weight.

Anti -foaming agent(s) can be included in the microparticle taste masking coat to reduce
25 frothing or foaming during manufacture ofthe coat. Anti-foaming agents useful for the coat
composition include, but are not liminted to simethicone, polyglycol, silicon oil, and mixtures thereof. In at least one embodiment the anti-foaming agent is Simethicone C. The anti
foaming agent can be present in an amount of from about 0.1% to about 10% ofthe microparticle taste masking coat weight including all values and ranges therebetween. For
30 example, in certain embodiments the anti-foaming agent is present in an amount offrom
about 0.2% to about 5%; in other embodiments from about 0.3% to about l%, and in still
other embodiments at about 0.6% by weight ofthe microparticle taste masking polymer dry weight.

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Plasticizer(s) can be included in the microparticle taste masking coat to provide increased flexibility and durability during manufacturing. Plasticizers that can be used in the microparticle taste masking coat of certain embodiments include acetylated monoglycerides; acetyltributyl citrate, butyl phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate;
dimethyl phthalate; ethyl phthalyl ethyl glycolate; glycerin; propylene glycol; triacetin; tripropioin; diacetin; dibutyl plithalate; acetyl monoglyceride; acetyltriethyl citrate,
polyethylene glycols; castor oil; rape seed oil, olive oil, sesame oil, triethyl citrate; polyhydric alcohols, glycerol, glycerin sorbitol, acetate esters, gylcerol triacetate, acetyl triethyl citrate,
10 dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, diisononyl pthalate, butyl octyl
phthalate, dioctyl azelate, epoxidized tallate, triisoctyl trimellitate, diethylhexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-decyl phthalate, di-n-undecyl phthalate, di-n-
tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-.etriyihexyl adipate, di-2-ethylhexyl
sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate,
15 diethylfumerate, dibutylsuccinate, diethylmalonate, clibutylphthaiate, dibutyisebacate,
glyceroltributyrate, and mixtures thereof. The plasticizer can be present in an amount of from about 1% to about 80% ofthe taste masking polymer thy weight including all values and,
ranges therebetween. For example, in certain embodiments the plasticizer is present in an
amount of from about 5% to about 50%, in other embodiments from about 10% to about
20 40%, and in still other embodiments at about 20% ofthe taste masking polymer dry weight.

The taste-masking coating can be present in an amount of from about 1% to about 90% by weight ofthe microparticle including all values and ranges therebetween, depending upon the choice ofpolymer, the ratio of polymer:pore former, and the total surface area ofthe
25 microparticle formulation. Since a certain thickness oftaste masking coating has to be
achieved in order to achieve effective taste masking, the amount oftaste masking polymer coating used during manufacture is related to the total surface area ofthe batch of uncoated micropartieles that requires a coating. The taste masking polymer surface area coverage can range from about 0.5 mg/cm2 to about 2 0mg/cm2 including all values and ranges
30 therebetween. For example, in certain embodiments the surface area coverage ofthe taste
masking polymer is from about 0.6 mg/cm2 to about 1 0mg/cm2, and in other embodiments is from about 1 mg/cm2 to about 5mg/cm2. In at least one embodiment ofthe invention, EUDRAG1Tfi E is employed as the taste masking polymer at a surface area coverage of

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about 4mg/cm2, One approach in estimating the total surface area of a multiparticulate batch is the permeability method according to Blame (ASTM Des. C 205-55), which is based upon the mathematical model of laminar flow through capillaries arranged in parallel,

In the absence of an accurate determination oftotal surface area of a microparticle, the
amount oftaste masking polymer to be applied can be expressed as a percentage ofthe
uncoated microparticle. For example, in certain embodiments the taste-masking coating is present in an amount of from about 5% to about 60% including all values and ranges therebetween; in other embodiments from about 10% to about 40%; and in still other
10 embodiments from about 15% to about 35% by weight ofthe microparticle. In at least one
embodiment the taste-masking coating is present in an amount of about 30% by weight ofthe microparticle.

In certain embodiments, the diameter ofthe microparticles (with or without the taste-masking
15 coating) range from about 50 urn to about 800 gm including all values and ranges
therebetween. For example, in certain embodiments the diameter ofthe microparticles range from about 100 to about 600 pm, and in other embodiments from about 150 urn to about
450 urn.

20 Microparticle Controlled Release Coat
The microparticles ofthe present invention can each be coated with at least one controlled
release coat. As used herein, the term "microparticle controlled release coat" refers to the
controlled release coat that substantially surrounds each microparticle. The microparticle Icontrolled release coat is designed to achieve a controlled release ofthe bupropion
25 hydrobrornide salt from the microparticle. For example, the microparticle controlled release
coat can be an enteric coat with low solubility at a gastric pH to reduce or minimize the drug release in the lumen of the stomach, whilst possessing pH dependent solubility to facilitate
drag release in the duodenum. In another embodiment, the controlled release coat can be a
delayed release coating that provides a delayed release ofthe bupropion hydrobromide salt
30 with a predetermined lagtime that is independent of, or alternatively dependent on, the pH of
the dissolution medium. For example, by increasing the thickness ofthe microparticle
controlled, release coat using a pH independent diffusion polymer, lagtirncs of about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours,

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about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours can be achieved. Alternatively, controlled release polymers can be selected that become soluble above a certain pH. Drug release from such a system is reduced or minimized until the certain pH for the polymer of choice is exceeded. With either approach, following the predetermined lag, drug is released, for example within about 1 hour for an immediate release pulse, or alternatively.over a prolonged period oftime, for example from about 3 to about 24 hours. In other embodiments, the microparticle controlled release coat can provide a
diffusion barrier that is independent ofpH, thus facilitating a sustained release profile, with substantially full release ofthe bupropion hydrobromide salt occurring in from about 3 to
10 about 24 hours following administration. In at least one embodiment, the microparticle
controlled release coat provides a delayed and sustained release ofthe bupropion
hydrobromide salt from the microparticle with substantially full release in about 24 hours following administration.

15 In certain embodiments, the microparticle controlled release coat can provide substantially
full release ofthe bupropion hydrobromide salt from the micro’article without requiring the
use of any pore formers. Unnecessary pore formers that are not required in the microparticle controlled release coat include hydrophilic polymers such as hydroxypropyl methylcellulose.

20 The microparticle controlled release coat includes at least one polymer in an amount
sufficient to achieve a controlled release ofthe bupropion hydrobromide salt. In at least one embodiment ofthe invention the controlled release polymer is an acrylic polymer. Suitable acrylic polymers include but are not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate,
5 aminoalkyl methacrylate copôlymer, poly(acrylic acid), poly(methactylic acid, methacrylic
acid ailcylamine copolymer, polymethyl methacrylate), poly(methacrylic acid) (anhydride), glycidyl methacrylate cdpolymers, and mixtures thereof.

In at least one embodiment the controlled release coat comprises polymerizable quaternary
30 ammoniurn compounds, ofwhich non-limiting examples include quaternized aminoalkyl
esters and aminoallcyl amides of acrylic acid and methacrylic acid, for example 3-methacryl-oxyethyl-trimethyl-ammonium methosulfate, 0-acryloxy-propyi-trimethyl-ammonium
chloride, trimethylaminomethyl-rnethacrylamide methosulfate and mixtures thereof. The

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quaternary ammonium atom can also be part of a heterocycle, as in methacryloxyethylmethyl-morpholiniom chloride or the corresponding piperidinium salt, or it can be joined to an acrylic acid group or a methacrylic acid group by way of a group containing hetero atoms, such as a polyglycol ether group. Further suitable polymerizable quaternary ammonium compounds include quaternized vinyl-substituted nitrogen
heterocycles such as methyl-vinyl pyridinium salts, vinyl esters of quaternized amino
carboxylic acids, and styryitriallcyl ammonium salts. Other polymerizable quaternary
ammonium compounds useful in the present invention include acryl- and methacryl-oxyethyltrimethyl-ammonium chloride and methosulfate, benzy1dimethylammoniurnethyl-
10 methacrylate chloride, dieth.ylmethylammoniumethyl-acrylate and -methacrylate
methosulfatc, N-trirnethylammoriiumpropylmethacrylamide chloride, N-

Sp trimethylammonium-2,2-dimethylpropyl- 1 -methacrylate chloride and mixtures thereof.

In at least one embodiment, the polymer ofthe controlled release coat is an acrylic polymer
15 comprised of one or more ammonio methacrylate copolymers. Aminonio methacrylate
copolymers (e.g. EUDRAGITfi RS and RL) are described in NF XVII as fully polymerized
copolymers of acrylic and methacrylic acid esters with a low content of quaternary
ammonium groups. In order to obtain a desirable dissolution profile for a given
therapeutically active agent such as bupropion hydrobrornide, it may be helpful in some
20 embodiments to incorporate two or more ammonia, methacrylate copolymers having differing
physical properties. For example, it is known that by changing the molar ratio ofthe
quaternary ammonium groups to the neutral (meth)acrylic esters, the permeability properties ofthe resultant controlled release coat can be modified.

25 In other embodiments ofthe present invention, the acrylic polymer coating further includes a
polymer whose permeability is pH dependent, such as anionic polymers synthesized from methacrylic acid and methacrylic acid methyl ester (e.g. EUDRAGITfi L and EUDRAGITfi
S). EUDRAGITfi L is insoluble in acids and pure water, but becomes increasingly
permeable above pH 5.0. EUDRAGITfi S is similar, except that it becomes increasingly
30 permeable above pH 7. The hydrophobic acrylic polymer coatings can also include a
polymer which is cationic in character based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters (e.g. EUDRAGITfi E). The hydrophobic acrylic polymer coatings of

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certain embodiments can further include a neutral copolymer based on poly (meth)acrylates, such as EUDRAGITfi NE

In other embodiments ofthe invention the controlled release polymer is a dispersion ofpoly
5 (ethylacrylate, methyl methacrylate) 2:1 (e.g. KOLLICOATfi EMM 30 D). In other
embodiments the controlled release polymer can be a polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as KOLLICOATfi SR30D. The dissolution profile can be altered by changing the relative amounts of different acrylic resin lacquers included in the coating. Also, by changing the molar ratio of polymerizable
10 permeability-enhancing agent (e.g., the quaternary ammonium compounds) in certain
embodiments to the neutral (meth)acrylic esters, the permeability properties (and thus the dissolution profile) ofthe resultant coating can be modified.

In at least one embodiment the controlled release polymer is ethylcellulose, which can be
15 used as a dry polymer (e.g. ETHOCELfi) solubilised in organic solvent prior to use, or as an
aqueous dispersion. One commercially available aqueous dispersion of ethylcellulose is AQUACOATfi. AQUACOATfi can be prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a
surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic
20 solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not
incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the
same as a coating, the AQUACOATfi is intimately mixed with a suitable plasticizer prior to
use. Another aqueous dispersion of ethylcellulose is SURELEASEfi. This product can be prepared by incorporating a plasticizer into the dispersion during the manufacturing process.
25 A hot melt of a polymer, plasticizer (e.g, dibutyl sebacate), and stabilizer (e.g, oleic acid) is
prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain
an aqueous dispersion which can be applied directly onto substrates.

Other examples ofpolymers that can be used in the microparticle controlled release coat
30 include cellulose acetate pbthalate, cellulose acetate trimaletate, hydroxy propyl
methylcellulose phthalate, polyvinyl acetatephthalate, polyvinyl alcohol phthalate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate,
sodium carmellose, calcium earmellose, sodium carboxymethyl starch, poly vinyl alcohol,

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hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, gelatin, starch, and cellulose based crosslinked polymers in which the degree of crosslinking is low so as to facilitate adsorption ofwater and expansion ofthe polymer matrix, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin,
5 pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable
hydrophilic polymers) polyhydroxyaLkyl methacrylate) (molecular weight from about 5k to
about 5000k), polyvinylpyrrolidone (molecular weight from about 10k to about 360k),
anionic and cationic hydrogels, zeiri, polyamides, polyvinyl alcohol having a low acetate
residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers ofmaleic
10 anhydride and styrene, ethylene, propylene or isobutylene, pectin (molecular weight from
about 30k to about 300k), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, POLYOXfi polyethylene oxides (molecular weight from about 100k
to about 5000k), AQUAKEEPfi acrylate polymers, diesters ofpolyglucan, crosslinked
polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, hydrophilic polymers such as
15 polysacchari.des, methyl cellulose, sodium or calcium carboxymethyl cellulose,
hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro
cellulose, carboxymethyl cellulose, cellulose ethers, methyl ethyl cellulose, ethyihydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, starch, maltodextrin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol
20 fatty acid esters, polyacrylamide, polyacrylic acid, natural gums, lecithins, pectin, alginates,
ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as arabic, karaya, locust bean, tragacanth, carrageens, guar, xanthan, seleroglucan
and mixtures and blends thereof.

25 In at least one embodiment the controlled release coat of the niicroparticles comprises

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polymers that can facilitate mucoadhsion within the gastrointestinal tract. Non-limiting
examples ofpolymers that can be used for mucoadhesion include carboxymethylcellulose, polyacrylic acid, CARBOPOLTM, PQLYCJJQPHJLTM, gelatin and other natural or synthetic polymers.

In at least one embodiment the microparticles are coated with a controlled release coat comprised of: at least one film-forming polymer which is insoluble in the liquids ofthe digestive tract, present in’ an amount offrom about 50% to about 90% including all values

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and ranges therebetween (e.g. from about 50% to about 80%) by weight of dry matter ofthe controlled release coat composition, and including at least one non-hydrosoluble cellulose derivate, (e.g. ethylcellulose, cellulose acetate, or mixtures thereof); at least one nitrogen-containing polymer, present in an amount of from about 2% to about 25% including all
5 values and ranges therebetween (e.g. from about 5% to about 15%) by weight of dry matter
ofthe controlled release coat composition, and including at least one polyacrylarnide, poly-N-vinylaride, poly-N-vinyl-iactame, polyvinylpyrrolidone, or mixtures thereof; optionally a plasticizer present in an amount of from about 2% to about 20% including all values and
ranges therebetween (e.g. from about 4% to about 15%) by weight of dry matter ofthe
10 controlled release coat composition, and including at least one ofthe following compounds:
glycerol esters, phtalates, citrates, sebacates, cetylalcohol esters, castor oil, cutiri, or mixtures thereof; at least one surface-active and/or lubricating agent, present in an amount offrom
about 2% to about 20% including all values and ranges therebetween (e.g. from about 4% to about 15%) by weight of dry matter ofthe controlled release coat composition, and chosen
15 from anionic surfactants such as the alkali metal and alkakine-earth metal salts offatty acids,
(e.g. stearic acid, oleic acid, and mixtures thereof), and/or from nonionic surfactants such as polyoxyethylenated esters ofsorbitan, polyoxyethylenated esters ofsorbitan,
polyoxyethylenated derivatives of castor oil, and/or from lubricants such as stearates (e.g, calcium, magnesium, aluminium, zinc stearate and mixtures thereof), stearylfumarates (e.g.
20 sodium stearylfimarate, glyceryl behenate and mixtures thereof); and mixtures thereof
wherein the coated microparticles are designed so as to be able to remain in the small
intestine for a period of at least about 5 hours; in certain embodiments at least about 7 hours;
and in certain other embodiments for a period of from about 8 hours to about 24 hours; so as
to allow absorption ofthe bupropion hydrobromide during at least part of its time in the small

25 intestine.

In a prophetic example of this embodiment ofthe invention,, the microparticics are coated in a fluidized bead coater with the following coating solution:
Ethyleellulose about 44.7g
30 PYP about 4.8g
Castor oil about 4.8g
Magnesium Stearate about 6.1 g
Acetone about 479g

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Isopranol about 53g

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In other embodiments ofthe present invention, the release of the bupropion hydrobromide from. a controlled release formulation can be further influenced, i.e., adjusted to a desired
rate, by the addition of one or more pore-formers to the controlled release coat, where the pore-formers can be inorganic or organic, and can include materials that can be dissolved, extracted or leached from the controlled release coat in the environment ofuse. Upon
exposure to fluids in the environment ofuse, the pore-formers are, for example, dissolved,
and channels and pores are formed that fill with the environmental fluid. For example, the
10 pore-formers can include one or more water-soluble hydrophilic polymers in order to modify
the release characteristics ofthe formulation. Non-limiting examples ofsuitable hydrophilic polymers include hydroxypropyhnetlhyicellulose, cellulose ethers and protein-derived
materials ofthese polymers, the cellulose ethers, (e.g. hydroxyalkylcelluloses and carboxyalkylcelluloses), and mixtures thereof. Also, synthetic water-soluble polymers can be
15 used, such as polyvinylpyrrolidone, cross-linked polyvinyl-pyrrolidone, polyethylene oxide,
water-soluble polydextrose, saccharides and polysaccharides, such as pullulan, dextran,
sucrose, glucose, fructose, mannitol, lactose, mannose, galactose, sorbitol, and mixtures
thereof. In at least one embodiment the hydrophilic polymer(s) include hydroxypropyl-
methylcellulose. Other examples ofpore-formers include alkali metal salts such as lithium
20 carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate,
potassium phosphate, sodium acetate, sodium citrate, and mixtures thereof. The pore-
forming solids can also be polymers which are soluble in the environment ofuse, such as
. CARBOWAXfi, CARBOPOLfi, and the like. The possible pore-formers embrace diols,
polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(a-w)alkylenediols, and
25 mixtures thereof Other pore-formers which can. be useful in the formulations ofthe present
invention include starch, modified starch, and starch derivatives, gums, including but not
limited to xanthan gum, alginic acid, other alginates, benitoniite, veegum, agar, guar, locust
bean gum, gum arabic, quince psyllium, flax seed, okra gum, arabinoglaetin, pectin,
tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked
30 polyvinylpynolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan,
kappa-carrageenan, lambda-earrageenan, gum karaya, biosynthetic gum, and mixtures
thereof. Other pore-formers include materials useful for making microporous lamina in the environment ofuse, such as polycarbonates comprised of linear polyesters of carbonic acid in

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which carbonate groups reoccur in the polymer chain, microporous materials such as bisphenol, a microporous polyvinylchloride), microporous polyamides, microporous modacrylic copolymers, microporous styrene-acrylic and its copolymers, porous polysulfones, halogenated polyvinylidene), polychioroethers, acetal polymers, polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylcne poiyol, poly(allcylenesulfldes), phenolics, polyesters, asymmetric porous polymers, cross-linked
olefin polymers, hydrophilic microporous hiomopolymers, copolymers or inteiolymers
having a reduced bulk density, and other similar materials, poly(urethane), cross-linked
chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated
10 proteins, semi-solid cross-linked poly(vinylpylTolldone), and mixtures thereof.

IInother embodiments a surfactant or an effervescent base can be included in the controlled release coat, which can reduce and in certain embodiments overcome surface tension effects.
In addition, the controlled release coat of certain embodiments can include one or more
15 osmagents (i.e., which can osmotically deliver the active agent from the device by providing
an osmotic pressure gradient against the external fluid, swelling agents (i.e., which can
include, but are not limited to hydrophilic pharmaceutically acceptable compounds with
various swelling rates in water), or other pharmaceutically acceptable agents (i.e., provided in
an amount sufficient to facilitate the entry ofthe environmental fluid without causing the
20 disruption ofthe impermeable coating). The surfactants that can be used in the controlled
release coat of certain embodiments can be anionic, cationic, nonionic, or amphoteric. Non-limiting examples ofsuch surfactants include sodium lauryl sulfate, Odium dodecyl sulfate, sorbitan esters, polysorbates, pluronics, potassium laurate, and mixtures thereof. Non-
limiting examples of effervescent bases that can be used in the controlled release coat of
25 certain embodiments include sodium glycine carbonate, sodium carbonate, potassium
carbonate, sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, and mixtures thereof. Non-limiting examples of osmagent:s that can be used in the controlled release coat
of certain embodiments include sodium chloride, calcium chloride, calcium lactate, sodium sulfate, lactose, glucose, sucrose, mannitol, area, other organic and inorganic compounds
30 known in the art, and mixtures thereof. The swelling agent can include, but is not limited to
at least one pharmaceutically acceptable hydrophilic compound, having a swelling rate or swelling amount in water at about 25°C that is: greater than or equal to at least about 10% by weight (wt/wt, greater than, or equal to at least about 15% by weight wt/wt), or greater than

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or equal to at least about 20% by weight (wt/wt). Non-limiting examples ofswelling agents
that can be used in the controlled release coat of certain embodiments ofthe present invention include crosslinked polyvinylpyrrolidones (e.g. polyplasdone, crospovidone and mixtures thereof), crosslinked carboxyalkylcelluloses, crosslinked carboxymethylcellulose (e.g.
5 crosslinked sodium croscarmellose), hydrophilic polymers of high molar mass (i.e., which
can be, but are not limited to being greater than or equal to 100,000 Daltons) which can
include, but are not limited to: polyvinyipyrrolidone(s), polyatkylene oxides (e.g.
polyethylene oxide, polypropylene oxide, and mixtures thereof), hydroxyalkylcelluloses (e.g. hydroxypropylcellulose, hydroxypropylmethylcellulose and mixtures thereof),
10 carboxyalkylcellulose (e.g. carboxymethylcellulose), modified starch (e.g. sodium glycolate),
starch or natural starch (e.g. corn., wheat, rice, potato and mixtures thereof), cellulose (i.e.
40 which can be, but is not limited to being in powder form or microcrystalline form), sodium
alginate, potassium polacriline, and corresponding blends or mixtures thereof. In other
embodiments, non-limiting examples ofthe swelling agent include the following sub-set of
15 compounds: crosslinked polyvinylpyrrolidone (e.g. polyplasdone, crospovidone or mixtures
thereof), crosslinked carboxyalkylcelluloses (e.g. crosslinked carboxymethylceiftiloses such
as crosslinked sodium croscarmellose), and mixtures thereof. In other embodiments, the
swelling agent can be a, nitrogen containing polymer, non-limiting examples of which can
include polyvinylpyrrolidone, crosslinked polyvinylpyrrolidone and mixtures thereof. The
20 concentration ofthe swelling agent in the controlled release coat of certain embodiments of
the present invention can be from about 3% to about 40% by weight ofthe microparticle
including all values and ranges therebetween. For example, in certain embodiments the
. concentration ofthe swelling agent in the controlled release coat is from about 4% to about
30%, and in other embodiments from about 5% to about 25% by weight ofthe microparticle.
25

In certain embodiments one or more pharmaceutically acceptable excipients consistent with
the objects ofthe present invention can be used in the controlled release coat, such as a
lubricant, an. emulsifying agent, an anti-foaming agent, and/or a plasticizer.

30 Lubricants can be included in the controlled release coat to help reduce friction of coated
microparticles during manufacturing. The lubricants that can be used in the controlled
release coat of certain embodiments ofthe present invention include but are not limited to adipic acid, magnesium stearate, calcium stearate, zinc stearate, calcium silicate, magnesium

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silicate, hydrogenated vegetable oils, sodium dhloride, sterotex, polyoxyethylene, glyceryl monostearate, talc, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stcaryl fumarate, light mineral oil, waxy fatty acid esters such as glyceryl behenate, (e.g. COMPRITOLT, STEAR-O-WET TMand MYVATEXTM TL. in at least one embodiment, the lubricant is selected from magnesium stoarate, talc and mixtures thereof. Combinations ofthese lubricants are operable. The lubricant can each be present in
an amount offrom about 1% to about 100% by weight ofthe controlled release coat dry
weight including all values and ranges therebetween. For example, in certain embodiments
wherein the controlled release polymer is ETJDRAGITfi NE3OD or EUDRAGITfi NE40J)
10 together with a hydrophilic pore former, the lubricant is present in an amount of from about
1% to about 30% by weight ofthe controlled release coat dry weight; in other embodiments

10 from about 2% to about 20%; and in still other embodiments at about 10% by weight ofthe
microparticle controlled release coat dry weight. In another embodiments where the
controlled release polymer is ethylcellulose (ETFIOCELTM FRI 00, PR45, PR20, PR1O or
15 PR7 polymer, or a mixture thereof), the Lubricant can be present in an amount of from. about
10% to about 100% by weight ofthe microparticle control-releasing coat dry weight; in
another embodiment from about 20% to about 80%; and in still another embodiments at
about 50% by weight ofthe microparticle control-releasing coat dry weight.

20 Emulsifying agent(s) (also called emulsifiers or ernulgents) can be included in the
microparticle controlled release coat to facilitate actual emulsification during manufacture of
the coat, and also to ensure emulsion stability during the shelf-life ofthe product.
Emulsifying agents useful for the microparticle control-releasing coat composition include,
but are not limited to naturally occurring materials and their semi synthetic derivatives, such
25 as the polysaccharides, as well as glycerol esters, cellulose ethers, sorbitan esters (e.g.
sorbitan monooleate or SPANTM 80), and polysorbates (e.g. TWEENTM 80). Combinations of emulsifying agents are operable. In at least one embodiment, the emulsifying agent is
TWEENTM 80. The emulsifying agent(s) can be present in an amount of from about 0.01% to about 5% by weight ofthe microparticle controlled release coat dry weight including all
30 values and ranges therebetween. For example, in certain, embodiments the emulsifying agent
is present in an amount offrom about 0,05% to about 3%; in other embodiments from about 0.08% to about 1.5%, and in still other embodiments at about 0.1% by weight ofthe microparticle controlled release coat dry weight.

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Anti-foaming agent(s) can be included in the microparticle controlled release coat to reduce frothing or foaming during manufacture ofthe coat. Anti-foaming agents useful for the coat composition include, but are not liminted to simethicone, polyglycol and silicon oil. In at
least one embodiment the anti-foaming agent is Simethiconc C. The anti-foaming agent can
be present in an amount of from about 0.1% to about 10% ofthe microparticle controlled release coat weight including all values and ranges therebetween. For, example, in certain embodiments the anti-foaming agent is present in an amount offrom about 0.2% to about
5%; in other embodiments from about 0.3% to about 1%, and in still other embodiments at
10 about 0.6% by weight ofthe microparticle controlled release coat dry weight.

Plasticizer(s) can be included in the microparticle controlled release coat to modify the
properties and characteristics ofthe polymers used in the coat for convenient processing
during manufacturing (e.g. provide increased flexibility and durability during manufacturing).
15 As used herein, the term "plasticizer" includes any compounds capable of plasticizing or
softening a polymer or binder used in the present invention. Once the coat has been manufactured, certain plasticizers can function to increase the hydrophilicity ofthe coat in the environment of use. During manufacture ofthe coat, the plasticizer can lower the melting
temperature or glass transition temperature (softening point temperature) ofthe polymer or
20 binder. The addition of a plasticizer, such as low molecular weight PEG, generally broadens
the average molecular weight of a polymer in which they are included thereby lowering its
glass transition temperature or softening point. Plasticizers can also generally reduce the
. viscosity of a polymer. Non-limiting examples ofplasticisers that can be used in the
microparticle controlled release coat include acetylated monoglyce’rides; acetyltributyl citrate,
25 butyl phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate; dimethyl phthalate; ethyl
phthalyl ethyl glycolate; glycerin; propylene glycol; triacet’in; tripropioin; diacetin; dibutyl
phthalate; acetyl monoglyceride; acetyltriethyl citrate, polyethylene glycols; castor oil; rape
seed oil, olive oil, sesame oil, triethyl citrate; polyhydric alcohols, glycerol, glycerin sorbitol,
acetate esters, gylcerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate,
30 butyl octyl phthalate, diisononyl phthalate, butyl octyl ’phthalate, dioctyl azelate, epoxidized
tallate, triiso ctyl trimellitate, diethyihexyl phthalate, di-n-octyl phthalate, di-i-o ctyl phthalate, di-i-decyl phthalate, di-n-undecyl phthalate, di-n-trideeyl phthalate, tri-2-ethylhexyl
trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di2-ethylhexyl azelate, dibutyl

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sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethyimalonate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, and mixtures thereof. The plasticizer can be present in an amount of from about 1% to about 80% ofthe controlled release coat dry weight including all values and ranges therebetween. For example, in certain embodiments
the plasticizer is present in an amount offrom about 5% to about 50%, in other embodiments
from about 10% to about 40%, and in still other embodiments at about 20% ofthe controlled
release coat dry weight.

The controlled release coat can be present in an amount offrom about 1% to about 100% by
10 weight ofthe microparticle including all values and ranges therebetween, depending upon the
choice ofpolymer, the ratio ofpolymer:pore former, and the total surface area ofthe

10 microparticle formulation. Since a certain thickness of controlled release coating has to be
achieved in order to achieve the desired dissolution profile, the amount of polymer coating
required during manufacture is related to the total surface area ofthe batch ofuncoated
15 microparticles that requires a coating. The controlled release polymer surface area coverage
can range from about 0.5 mg/cm2 to about 30mg/cm2 including all values and ranges
therebetween. For example in certain embodiments the surface area coverage ofthe
controlled release polymer is from about 0.6 mg/cm2 to about 20mg/cm2, and in other embodiments from about 1 mg/cm2 to about 5mg/cm2. In at least one embodiment ofthe
20 invention, EUDRAGITfi NE30D is used as the controlled release polymer at a surface area
coverage of about 10mg/cm2. One approach to estimate the total surface area of a multiparticulate batch is the permeability method according to Blame (ASTM Des. C 205-
55), which is based upon the mathematical mOdel of laminar flow through capillaries
arranged in parallel. In the absence of an accuracte determination oftotal surface area of a
25 microoparticle, the amount of controlled release polymer to be applied can be expressed as a
percentage ofthe uncoated microparticle.

The controlled release polymer can be present in an amount offrom about 1% to about 99%
by weight ofthe coated microparticle including all values and ranges therebetween,
30 depending on the controlled release profile desired. For example, in certain embodiments the
polymer is present in an amount offrom about 5% to about 80%, and in other embodiments
from about 10% to about 50% by weight ofthe coated microparticle. In at least one
embodiment wherein the controlled release polymer is EUDRAGITfi NE30D, EUDRAGITfi

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NE40D, KOLLICOATfi SR 30D, or a mixture thereof, the polymer is present in an amount offrom about 1% to about 50% -in other embodiments from about 5% to about 30%; and in still other embodiments is about 15% by weight ofthe coated microparticle. In at least one embodiment wherein the controlled release polymer is ethylcellulose, the polymer is present
in an amount of from about 1% to about 99% by weight ofthe coated microparticle; in other embodiments from about 5% to about 50%; and in still other embodiments at about 20% by weight ofthe coated microparticle. In at least one embodiment wherein the controlled release polymer is ETHOCELTM, an ethyl cellulose grade PRIM, PR45, PR20, PR1O, PR7 polymer,
or a mixture thereof, the polymer is present in an amount of from about 5% to about 30% by
10 weight ofthe coated microparticle; in other embodiments from about 10% to about 25%; and
in still other embodiments at about 20% by weight ofthe coated microparticle.

In certain embodiments, the diameter ofthe microparticles (with or without the controlled
release coat) can range from about 50 trn to about 800 tm including all values and ranges
15 therebetween. For example, in certain embodiments the diameter ofthe microparticles range
from about 100 tm to about 600 tm, and in other embodiments from about 150 pm to about 450.trn,

It is contemplated that in alternative embodiments, other excipients consistent with the
20 objects ofthe present invention can also be used in the microparticle controlled release coat.

In at least one embodiment, the microparticle controlled release coat includes about 96% EUDRAGITfi NE30D, about 1.9% Magnesium stearate, about 1.9% Talc, about 0.04% TWEENfi 80, and about 0.19% Simethicone C, when expressed as percentage by weight of
25 the dry controlled release coat composition. In another embodiment, the microparticle
controlled release coat includes about 68% ethylcellulose about 17% glyceryl monostearate
and about 15% acetyl tributylcitrate when expressed as percentage by weight ofthe dry controlled release coat composition.

30 In certain embodiments the microparticle controlled release coat can be made according to
any one ofthe methods described herein.

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The manufacturing process for the microparticle controlled release coat can be as follows.
Water is split into two portions of about 15% and about 85%. The anti-foaming agent and the emulsifying agent are then added to the 15% water portion, and mixed at about 300 rpm to
form portion A. In at least one embodiment, the anti-foaming agent is Simethicone C, and
5 the emulsifying agent is TWEEMTM 80. A first lubricant is then added to the 85% water
portion and mixed at about 9500 rpm to form portion B. In at least one embodiment, the first lubricant is talc. Then portion A is mixed with portion B, a second lubricant is slowly added,
and mixed at about 700 rpm overnight. In at least one embodiment, the second lubricant is magnesium stearate. Finally, an aqueous dispersion of a neutral ester copolymer is added and
10 mixed for about 30 minutes at about 500 rpm. In at least one embodiment, the aqueous
dispersion of a neutral ester copolymer is EUDRAGITfi NE30D. The resultant controlled release Coat solution can then be used to coat the niicroparticles to about a 35% weight gain
with the following parameters: An inlet temperature offrom about 10°C to about 60°C
including all values and ranges therebetween, in certain embodiments from about 20°C to
15 about 40°C, and in at least one embodiment from about 25°C to about 35°C; an outlet
temperature of from about 10°C to about 60°C including all values and ranges therebetween,
in certain embodiments from about 20°C to about 40°C, and in at least one embodiment from about 25°C to about 35°C; a product temperature offrom about 10°C to about 60°C including
all values and ranges therebetween, in certain embodiments from about 15°C to about 35°C,
20 and in at least one embodiment from about 22°C to about 27°C; an air flow of from about 10
cmlh to about 180 c.mlli including all values and ranges therebetween, in certain
embodiments from about 40 c.m/h to about 120 c,mlh, and in at least one embodiment from about 60 c.nilh to about 80 c.m/h; and an atomizing pressure of from about 0.5 bar to about
4.5 bar including all values and ranges therebetween, in certain embodiments from about 1
25 bar to about 3 bar, and in at least one embodiment at about 2 bar. The resultant controlled
release coated microparticles can then be discharged from the coating chamber and oven
cured with the following parameters: A curing temperature offrom about 20°C to about 65°C including all values and ranges therebetween, in certain embodiments from about 30°C to
about 55°C, and in at least one embodiment at about 40°C; and a curing time of from about 2
30 hours to about 120 hours including all values and ranges therebetween, in certain
embodiments from about 10 hours to about 40 hours, and in at least one embodiment at about
24 hours. Any other technology resulting in the formulation of the micropartiele controlled release coat consistent with the objects ofthe invention can also be used.

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Microparticle Dosage Forms

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Highly useful dosage forms result when microparticles made from compositions containing a bupropion hydrobromide salt, spheronization aids, and other excipient(s) are coated with controlled release polymer(s). The controlled release coated microparticles can then be combined with an excipient mass and/or other pharmaceutical excipients, and compressed
into tablets. Conventional tablets can be manufactured by compressing the coated
microparticles with suitable excipients using known compression techniques. The dissolution profile ofthe controlled release coated multiparticles is not substantially affected by the
10 compression ofthe microparticles into a tablet. The resultant dosage forms enjoy the
processing ease associated with the use of excipient masses and the release properties
associated with controlled release coated microparticles. Alternatively, the coated
microparticles can be filled into capsules.

15 The fomis of administration according to the invention are suitable for oral administration.
In certain embodiments the forms of administration are tablets and capsules. However, the composition ofthe invention can also take the form of pellets, beads or microtablets, which
can then be packaged into capsules or compressed into a unitary solid dosage form. Other
solid oral dosage forms as disclosed herein can be prepared by the skilled artisan, despite the
20 fact that such other solid oral dosage forms may be more difficult to commercially
manufacture.

The present invention also contemplates combinations of differently coated microparticles
into a dosage form to provide a variety of different release profiles. For example, in certain
25 embodiments, microparticles with a delayed release profile can be combined with other
microparticles having a sustained release profile to provide a multiple component controlled release bupropion formulation. In addition, other embodiments can include one or more
further components ofimmediate release bupropion. The immediate release bupropion component can take the form of uncoated bupropion microparticles or powders; bupropion
30 microparticles coated with a highly soluble immediate release coating, such as an
OPADRYfi type coating, as are known to those skilled in the art, or a combination of any of
the foregoing. The multiple components can then be blended together in the desired ratio and

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placed in a capsule, or formed into a tablet. Examples ofmultiple component controlled release bupropion formulations are described in US 6,905,708.

Dose Sipping Technology
5 The present invention also contemplates an oral delivery system for delivering microparticles
containing bupropion hydrobromide in admixture with a fluid. For example, an oral delivery
system is provided which comprises a hollow drug formulation chamber. In at least one
embodiment, the chamber has a first end and a second end and contains a formulation in the
form ofmicroparticles. The drug formulation comprises bupropion hydrobromide. The
10 system further comprises a fluid passing drug formulation retainer in the first end ofthe
chamber. The retainer prevents release ofthe microparticles from the first end while Spermitting fluid entry into the chamber. In other embodiments, the microparticles contained within the chamber comprise bupropion hydrobromide and at least one other drug.

15 Certain embodiments ofthe present invention further provide a method for orally delivering
microparticles containing bupropion hydrobromide formulation in admixture.with a fluid.
The method involves inserting microparticles of bupropion hydrobromide formulation into a
hollow drug delivery chamber of a drug delivery device. The chamber has a first end and a
second end. The first end of the chamber has a fluid passing drug formulation retainer. The
20 drug delivery device has a first and second end. Th first end ofthe drug delivering device is
inserted into a fluid and the second end is inserted into the mouth of a patient. The patient
then applies suction to the second end ofthe device to cause delivery ofthe fluid and microparticles ofbupropion hydrobromide formulation into the patient’s mouth.

25 The term "drug formulation retainer" as used herein, refers to a valve, plug or restriction, or
the like that prevents passage ofthe drug formulation from the device. By "fluid passing drug formulation retainer" is intended a valve, plug or restriction or the like that allows for passage offluids but does not allow for passage of other ingredients such as the drug formulation that
is contained in the delivery device.
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The dispensing device ofthis embodiment ofthe invention finds use where it is inconvenient
or unsafe to use solid oral dosage forms such as capsules or tablets. The devices can be particularly useful in geriatric or pediatric patient populations but they can also be useful for

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those who have difficulty swallowing capsules or tablets. A single delivery device or several devices can be administered to a patient during a therapeutic program.

Generally the device is in prepared form prior to placement in a fluid. In at least one
5 embodiment the dispensing device comprises a hollow drug formulation chamber with a first
end and a second end. Contained within the chamber are drug formulation and fluid passing drug formulation retainers. The fluid passing drug formulation retainer comprises a
restriction and a one-way plug. The diameter ofthe opening is smaller than the plug. In at
least one embodiment the restriction is made by crimping an end of the chamber. The second
10 end of the chamber has a drug formulation retainer for preventing release ofthe plug. In at
least one embodiment the retainer is prepared by crimping the end ofthe chamber.
Microparticles of bupropion hydrobromide are then placed in the chamber. An end-cap is
placed over the second end ofthe chamber prior to use to prevent release ofthe drug formulation. In prepared form, the plug substantially seals the first end ofthe chamber,
15 thereby preventing loss ofthe drug formulation from the first end.

The device can be formed from any suitable material that is physically and/or chemically
compatible with both the active drug and the liquid diluent to be mixed therein. In certain embodiments, representative materials for forming devices including the drug formulation
20 chamber, the elongated tubular member, the end caps and tabs, include, without limitation,
paper, plastic such as propylene/styrene copolymers, polyproylene, high density
polyethylene, low density polyethylene and the like. The devices can have an inner diameter
. offrom about 3 mm to about 8 mm including all values and ranges therebetween, and a wall
thickness of from about 0.1 mm to about 0.4 mm including all values and ranges
25 therebetween. The devices can be from about 10 cm to about 30 cm in length including all
values and ranges therebetween.

The fluid passing drug formulation retainer permits the free flow ofliquid medium but
prohibits passage ofthe drug formulation from the device prior to delivery. Where the
30 retainer comprises a one-way plug or valve, the plug or valve will seal the saw at
atmospheric pressure. When suction is applied, fluid will be drawn around the plug and into
the drug formulation chamber. Further, the plug has a density of less than one so that it will ascend to the top as the drug formulation is delivered into the oral cavity. When suction is no

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longer applied, the plug will remain in the highest position it reached during sipping. The
plug can be prepared from closed cell polyethylene foam such as ETHAFOAMfi. Other
forms of one way plugs can be a balloon of elastomeric material, a one-way mechanical ball valve and the like.

Examples offluid that can be used for suspending the drug formulation by sipping through the drug formulation chamber include any palatable liquid such as water, juice, milk, soda, coffee, tea etc. Care must be taken to ensure compatibility of the fluid with the drug formulation.

In at least one embodiment, a dose sipping delivery device according to the present invention can be prepared as follows. Jumbo size straws with an inside diameter of about 0.21 inches
and a length of about 8 inches are heat sealed at one end. The seal is partially cut offso that
the "one-way" plug cannot escape. The partially sealed end is enclosed by half of a size 1
15 hard gelatin capsule. Micropartieles are then placed inside the open end ofthe straw. A
"one-way" plug made of closed cell polyethylene foam (e.g. MICROFOAMfi) is trimmed to snugly fit inside the straw. The plug is then placed inside the straw, on top ofthe
microparticles. During operation, the plug end of the straw is placed into a glass ofwater and
the protective gelatin capsule on the top ofthe straw is removed. By slowly applying suction
20 through the partially sealed end ofthe straw, the microparticles are sucked into the mouth and
easily swallowed.

Osmotic Dosage Forms
Osmotic dosage forms, osmotic delivery devices, modified release osmotic dosage forms, or
25 osmosis-controlled extended-release systems are terms used interchangeably herein and are
defined to mean dosage forms which forcibly dispense the bupropion hydrobromide salt by pressure created by osmosis or by osmosis and diffusion offluid into a material which
expands and forces the bupropion hydrobrornide salt to be dispensed from the osmotic dosage form. Osmosis can be defiied as the flow ofsolvent from a compartment with a low
30 concentration of solute to a compartment with a high concentration ofsolute. The two
compartments are separated by a membrane, wall, or coat, which allows flow ofsolvent (a
liquid, aqueous media, or biological fluids) but not the solute. Non-limiting examples ofsuch membranes include a semipermeable membrane, microporous, asymmetric membrane, which

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asymmetric membrane can be permeable, semipermeable, perforated, or unperforated. Such membrane can deliver the bupropion hydrobromide salt by osmotic pumping, diffusion or the combined mechanisms of diffusion and osmotic pumping. Thus, in principle, osmosis
controlled release ofthe bupropion hydrobromide salt involves osmotic transport of an
5 aqueous media into the osmotic dosage form followed by dissolution ofthe bupropion

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hydrobromide salt and the subsequent transport ofthe saturated solution ofthe bupropion hydrobromide salt by osmotic pumping ofthe solution through at least one passageway in the semipermeable membrane or by a combination of osmosis and diffusion through the semipermeable membrane.

It is well known to one of ordinary skill in the art that the desired in-vitro release rate and the in-vivo pharmacokinetic parameters can be influenced by several factors, such as for
example, the amount ofthe bupropion hydrobromide salt used to form the core, the amount ofpharmaceutically acceptable excipient used to form the core, the type of pharmaceutically
15 acceptable excipient used to form the core, the amount or type of any other materials used to
form the core such as, for example, osmagents (the term osmagent, osmotically effective
salutes, osmotically effective compound and osmotic agents are used interchangeably herein) osmopolymers, and any combination thereof. The release profile can also be influenced by.
the material used to form the semipermeable membrane covering the core or by the material
20 used to form any coating, such as a controlled release coating. With these factors in mind, an
osmotic device can therefore be designed to exhibit an in-vitro release rate such that in
certain embodiments, after about 2 hours from about 0 to about 20% by weight of the
. bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45%
by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about
25 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about
16 hours, more than about 80% by weight ofthe bupropion hydrobomide salt is released,
when measured for example by using a LISP Type 1 apparatus (Rotating Basket Method) in
900m1 water, 0.1N HC1, 0. IN HC1 + 0.1% Cetrimide, USP Buffer PH 1.5, Acetate Buffer pH
4.5, Phosphate Buffer, pH 6.5 or Phosphate Buffer pH 7.4 at 75 rpm at 37°C – 0.5°C.
30 Alternatively dissolution may be effected in USP-3 media such as SGF pH 1.2, Acetate
Buffer at pH 4.5 or phosphate buffer at pH 6.8.

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Osmotic devices also may be designed to achieve an in-vitro release of no more than about 40% after about 2 hours, from about 40% to about 75% release after about 4 hours, at least about 75% after about 8 hours, and at least about 85% after about 16 hours when assayed using a dissolution medium such as identified above or known in the art.

In certain embodiments ofthe present invention, an osmotic dosage form is provided having
a core comprising the bupropion hydrobromide salt and one or more excipients. In at least
one embodiment the osmotic dosage form comprises an osmagent. The osmotic delivery
system for example, can be in the form of a tablet or capsule containing microparticles.

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In certain embodiments, the core ofthe osmotic dosage form comprises a water sweilable

10 polymer, non-limiting examples ofwhich include hydroxypropyl cellulose, alkylceliulose,
hydroxyalkyiceilutose, polyalkylene oxide, polyethylene oxide, and mixtures thereof. A
binder can be included in the core of certain embodiments of the osmotic dosage form to
15 increase the core’s mechanical strength. Non-limiting examples of binders include polyvinyl
pyrollidine, carboxyvinyl polymer, methylceilulose, hydroxyethylcellulose, hydroxypropylceflulose, hydroxypropylmethylceilulose, a low molecular weight polyethylene
oxide polymer, hydroxypropylmethylcellulose, dextrin, maltodextrin, gelatin, polyvinyl
alcohol, xanthan gum, carbomers, caragheen, starch derivatives, and mixtures thereof.
20 Lubricants can be included in certain embodiments ofthe osmotic dosage form to provide
decreased friction between the solid and die wall during tablet manufacturing. Non-limiting examples of lubricants include stearic acid, magnesium stearate, glyceryl behenate, talc,
mineral oil, sodium stearyl funiarate, hydrogenated vegetable all, sodium beuzoate, calcium stearate, and mixtures thereof, in other embodiments, additional inert excipients consistent
25 with the objects ofthe invention can also be included in the core ofthe osmotic dosage form

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to facilitate the preparation and/or improve patient acceptability ofthe final osmotic dosage form as described herein. Suitable inert excipients are well known to the skilled artisan and
can be found in the relevant literature, for example in the Handbook of Pharmaceutical Excipients (Rowe et. al., 4th Ed,, Pharmaceutical Press, 2003).

In at least one embodiment, a modified release osmotic dosage form comprises bupropion hydrobromide in a therapeutically effective amount, which releases the bupropion hydrobromide by forcibly dispensing the bupropion hydrobromide from a core via a

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semipermeable membrane by diffusion and/or at least one passageway in the membrane by osmotic pumping (i) all or in part by pressure created in the core by osmosis i.e., positive hydrostatic pressure of a liquid, solvent, biological fluid or aqueous media and/or all or in
part by the expansion of a swellable material which forces the bupropion hydrobromide to be
5 dispensed from the core ofthe dosage form, and (ii) is formulated such thatthe dosage form
exhibits an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after about 8 hours,
from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and
10 after about 16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is
released.

In at least one embodiment, the modified release dosage form comprises an osmotic delivery device comprising a homogenous solid core comprising substantially the bupropion
15 hydrobromide salt present in a therapeutically effective amount with at least one
pharmaceutically acceptable excipient, said core surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery of the bupropion hydrobromide salt from the core to the exterior ofthe dosage form through at least one passageway or by a combination of osmosis and diffusion such that the dosage form exhibits
20 an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight
ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from
about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is
25 released. In at least one such embodiment the in-vitro release rate ofthe bupropion
hydrobromide salt is such that after about 2 hours no more than about 40% is released, after about 4 hours from about 40% to about 75% is released, after about 8 hours at least about
75% is released, and after about 16 hours at least about 85% is released.

30 In at least one embodiment, the modified release dosage form comprises a multiparticulate
dosage form, each microparticle comprising an osmotic delivery device, each microparticle comprising a homogenous solid core comprising substantially the bupropion hydrobromide
salt with at least one pharmaceutically acceptable excipient, said core of each microparticle

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surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery of the bupropion hydrobromide salt from the core to the exterior ofthe dosage form through a plurality ofpores formed in the semipermeable membrane by inclusion of a pore forming agent in the membrane or by a combination of osmosis and
diffusion so as to allow communication ofthe core with the outside ofthe device for delivery ofthe bupropion hydrobromide salt and is formulated such that the dosage form comprises a therapeutically effective amount ofthe bupropion hydrobrornide salt and exhibits an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45%
10 by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about
40% to about 90% by weight of the bupropion hydrobromide salt is released, and after about
16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is released. In
at least one such embodiment the in-vitro release rate ofthe bupropion hydrobromide salt is
such that after about 2 hours no more than about 40% is released, after about 4 hours from
15 about 40% to about 75% is released, after about 8 hours at least about 750Zo is released and
after about 16 hours at least about 85% is released.

In at least one embodiment, the modified release dosage form comprises a multiparticulate dosage form, each microparticle comprising an osmotic delivery device, each microparticle
20 comprising a homogenous solid core comprising substantially the bupropion hydrobromide
salt in admixture with at least one pharmaceutically acceptable excipient, an osmagent and/or
an osmopolymer, said core of each niicroparticle surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery ofthe bupropion hydrobromide salt from the core to the exterior ofthe dosage form through a plurality of
25 pores formed in the semipermeable membrane by inclusion of a pore forming agent in the
membrane or by a combination of osmosis and by diffusion so as to allow communication of
the core with the outside ofthe device for delivery ofthe bupropion hydrobromide salt and is formulated such that the dosage form comprises a therapeutically effective amount ofthe bupropion hydrobromide salt and exhibits an in-vitro release rate such that after about 2 hours
30 from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after
about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of

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the bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro release rate ofthe bupropion hydrobromide salt is such that after about 2 hours no more than about 40% is released, after about 4 hours from about 40% to about 75% is released, after about 8 hours at least about 75% is released and after about 16 hours at least about 85% is
5 released.

In at least one embodiment, the modified release dosage form comprises a multiparticulate dosage form, each microparticle comprising a homogenous solid core comprising
substantially the bupropion hydrobromide salt with at least one pharmaceutically acceptable
10 excipient in admixture with an osmagent, and/or an osmopolymer, and/or an absorption
enhancer, said rnicroparticles compressed into a tablet together with at least one pharmaceutically acceptable excipient, said tablet surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery ofthe bupropion hydrobromide salt from the tablet interior to the exterior ofthe dosage form through at least
15 one passageway in the semipermeable membrane and/or by diffusion, through the
semipermeable membrane so as to allow communication ofthe tablet interior with the
exterior ofthe tablet for delivery ofthe bupropion hydrobromide salt and is formulated such
that the dosage form comprises a therapeutically effective amount ofthe bupropion
hydrobromide salt and exhibits an in-vitro release rate such that after about 2 hours from
20 about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about
4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is
released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of
the bupropion hydrobromide salt is released. in at least one such embodiment the in-vitro
25 release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more
than about 40% is released, after about 4 hours from about 40% to about 75% is released,
after about 8 hours at least about 75% is released, and after about 16 hours at least about 85%
is released.

30 In at least one embodiment, the modified release dosage form comprises a multiparticulate
dosage form, each microparticle comprising a sugar sphere or nonpareil bead coated with at
least one layer comprising substantially the bupropion hydrobromide salt with at least one pharmaceutically acceptable excipient, said at least one layer surrounded by a semipermeable

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membrane which permits entry of an aqueous liquid into the layer and delivery ofthe bupropion hydrobromide salt from the layer to the exterior ofthe dosage form through a plurality of pores formed in the semipermeable membrane by inclusion of a pore forming agent in the membrane and/or by diffusion so as to allow communication ofthe core with the outside ofthe device for delivery ofthe bupropion hydrobromide salt and is formulated such
that the dosage form comprises a therapeutically effective amount ofthe bupropion hydrobromide salt and exhibits an in-vitro release rate such that after about 2 hours from
about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about
4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is
10 released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion
hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of
the bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro
release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more
than about 40% is released, after about 4 hours from about 40% to about 75% is released,
15 after about 8 hours at least about 75% is released and after about 16 hours at least about 85%
is released.

In at least one embodiment, the modified release dosage form comprises a m-ultiparticulate
dosage form, each microparticle comprising a sugar sphere or nonpareil bead coated with at
20 least one layer comprising substantially the bupropion hydrobromide salt in admixture with at
least one pharmaceutically acceptable excipient, an osmagent and/or an osmopolyrner, said at least one layer surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the layer and delivery ofthe bupropion hydrobromide salt from the layer to the exterior ofthe dosage form through a plurality of pores formed in the semipermeable
25 membrane by inclusion of a pore forming agent in the membrane and/or by diffusion so as to
allow communication of the core with the outside ofthe device for delivery ofthe bupropion hydrobromide salt and is formulated such that the dosage form comprises a therapeutically effective amount ofthe bupropion hydrobromide salt and exhibits an in-vitro release rate
such that after about 2 hours from about 0% to about 20% by weight of the bupropion
30 hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight of
the bupropion hydrobromide salt is released, after about 8 hours, from about 40% to about
90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours,
more than about 80% by weight ofthe bupropion hydrobromide salt is released. In at least

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one such embodiment the in-vitro release profile of bupropion hydrobromide salt is such that after about 2 hours no more than about 40% is released, after about 4 hours from about 40% to about 75% is released, after about 8 hours at least about 75% is released and after about 16 hours at least about 85% is released.

In at least one embodiment, the modified release dosage form comprises a modified release osmotic dosage form comprising a homogenous core comprising a therapeutically effective amount ofthe bupropion hydrobromide salt in admixture with an osmagent, and/or an osmopolymer, and/or and absorption enhancer, said core surrounded by a nontoxic wall,
10 membrane or coat, such as for example a semipermeable membrane which permits entry of
an aqueous liquid into the core and delivery ofthe bupropion hydrobromide salt from the
core to the exterior ofthe dosage form through at least one passageway in the semipermeable membrane and/or by diffusion through the membrane so as to allow communication ofthe
core with the outside ofthe dosage form for delivery ofthe bupropion hydrobromide salt and
15 is formulated such that the dosage form exhibits an in-vitro release rate such that after about 2
hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide
salt is released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of
20 the bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro

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release profile of bupropion hydrobromide salt is such that after about 2 hours no more than
about 40% is released, after about 4 hours from about 40% to about 75% is released, after
about 8 hours at least about 75% is released and after about 16 hours at least about 85% is released.

In at least one embodiment the modified release dosage form comprises an osmotic delivery device comprising the bupropion hydrobromide salt present in a therapeutically effective
amount in a layered, contacting arrangement with a swellable material composition to yield a solid core with two or more layers, which core is surrounded by a nontoxic wall, membrane
30 or coat, such as for example a semipermeable membrane which permits entry of an aqueous
liquid into the core and delivery ofthe bupropion hydrobromide salt from the core to the
exterior ofthe dosage form through at least one passageway in the semipermeable membrane
or by osmosis and diffusion through the membrane so as to allow communication ofthe core

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with the outside of the dosage form for delivery of the bupropion hydrobromide salt and is formulated such that the dosage form exhibits an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide
5 salt is released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion
hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of
the bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro
release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more
than about 40% is released, after about 4 hours about 40% to about 75% is released, after
10 about S hours at least about 75% is released and after about 16 hours at least about 85% is
released.

In at least one embodiment, the modified release dosage form comprises an osmotic delivery device comprising a core and a membrane surrounding said core, said core comprising a
15 therapeutically effective amount ofthe bupropion hydrobromide salt, and optionally at least
one means for forcibly dispensing the bupropion hydrobromide salt from the device, said membrane comprising at least one means for the exit ofthe bupropion hydrobromide salt
from the device, said device formulated such that when the device is in an aqueous medium,
the bupropion hydrobromide salt, and optionally the at least one means for forcibly
20 dispensing the bupropion hydrobromide salt from the device and the at least one means for
the exit ofthe bupropion hydrobromide salt from the device cooperatively function to exhibit
an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after about S hours, from
25 about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after
about 16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is
released. In at least one such embodiment the in-vitro release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more than about 40% is released, after about 4 hours fi-om about 40% to about 75% is released, after about S hours at least about
30 75% is released and after about 16 hours at least about 85% is released.

In at least one embodiment, the modified release dosage form comprises an osmotic delivery device comprising a core and a membrane surrounding said core, said core comprising a

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therapeutically effective amount ofthe bupropion hydrobromide salt, at least one means for increasing the hydrostatic pressure inside the membrane and optionally at least one means for forcibly dispensing the bupropion hydrobromide salt from the device, said membrane comprising at least one means for the exit ofthe bupropion hydrobromide salt from the
device, said device formulated such that when the device is in an aqueous medium, the at
least one means for increasing the hydrostatic pressure inside the membrane, and optionally
the at least one means for forcibly dispensing the bupropion hydrobromide salt from the
device and the at least one means for the exit ofthe bupropion hydrobromide salt
cooperatively function to exhibit an in-vitro release rate such that after about 2 hours from
10 about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about
4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is

5 released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion
hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of
the bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro
15 release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more
than about 40% is released, after about 4 hours from about 40% to about 75% is released,
after about 8 hours at least about 75% is released and after about 16 hours at least about 85%
is released.

20 Certain embodiments ofthe invention are directed to once-a-day bupropion hydrobromide
sustained release formulations that are bioequivalent according to FDA guidelines to
WELLBUTRINTM ER or ZYBANTM/WELLBUTRNTM SR when administered once-daily to

Sasubject in need thereof and wherein the bupropion hydrobromide salt contained is more stable than an equivalent molar amount ofthe bupropion hydrochloride salt contained in
25 WELLBIJTRINTM ER or ZYBANTM when exposed to like conditions, for example when
stored for 10 days, 13 days, 14 days, 20 days, 24 days, 1 month, 2 months, 3 months, 4
months, 5 months, 6 months, or more under accelerated storage conditions (e.g. 40 degrees C,
75% relative humidity). In at least one embodiment the invention encompasses 174mg,
348mg and 522mg bupropion hydrobromide formulations that are bioequivalent to bupropion
30 hydrochloride formulations.

At least one embodiment is directed to topical formulations containing bupropion
hydrobromide that can be administered topically, e.g., transmucosally or transdermally.

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Particularly, the at least one embodiment embraces topically administrable gels and patch
type delivery devices which can comprise another active agent such as nicotine.

At least one embodiment is directed to inhalable pulmonary deliverable compositions
5 containing bupropion hydrobromide that can be administered via pulmonary delivery to a
subject in need thereof. These compositions can be produced according to the aerosol
technology as known in the art.

At least one embodiment is directed to injectable compositions comprising an effective
10 amount of bupropion hydrobromide and a pharmaceutically acceptable carrier or excipient.

SAtleast one embodiment is directed to a method oftreating a condition comprising

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administering any one ofthe above described osmotic dosage forms to a patient in need of
such administration once-daily.

At least one embodiment is directed to a method for administering a bupropion hydrobromide
salt to the gastrointestinal tract of a human for the treatment or management of a condition,
wherein the method comprises: (a) admitting orally into the human a modified release dosage form comprising a bupropion hydrobromide salt, the modified release dosage form
20 comprising an osmotic dosage form; and (b) administering the bupropion hydrobromide salt
from the osmotic dosage form in a therapeutically responsive dose to produce the treatment
or management of the condition such that the osmotic dosage form exhibits an in-vitro release
rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight of
25 the bupropion hydrobromide salt is released, after about 8 hours, from about 40% to about
90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours,
more than about 80% by weight ofthe bupropion hydrobromide salt is released. In at least
one such embodiment the in-vitro release profile ofthe bupropion hydrobromide salt is such
that after about 2 hours no more than about 40% is released, after about 4 hours from about
30 40% to about 75% is released, after about 8 hours at least about 75% is released and after
about 16 hours at least about 85% is released.

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At least one embodiment is directed to a method for administering a bupropion hydrobromide salt to the gastrointestinal tract of a human for the treatment or management of a condition, wherein the method comprises: (a) admitting orally into the human a modified release dosage form comprising a core and a membrane surrounding said core, said core comprising the
5 bupropion hydrobromide salt and optionally a means for forcibly dispensing the bupropion
hydrobromide salt from the device, said membrane comprising at least one means for the exit ofthe bupropion hydrobromide salt from the dosage form, and () administering the
bupropion hydrobromide salt from the dosage form which is formulated such that when the dosage form is in an aqueous medium, the bupropion hydrobromide salt and optionally the
10 means for forcibly dispensing the bupropion hydrobromide salt and the at least one means for
the exit ofthe bupropion hydrobromide salt cooperatively function to exhibit an in-vitro
release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45%
by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about
15 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about
16 hours more than about 80% by weight ofthe bupropion hydrobromide salt is released, in
at least one such embodiment the in-Vitro release profile ofthe bupropion hydrobromid-e salt
is such that after about 2 hours no more than about 40% is released, after about 4 hours from
about 40% to about 75% is released, after about 8 hours at least about 75% is released and
20 after about 16 hours at least about 85% is released.

At least one embodiment is directed to a method for administering a bupropion hydrobromide
. salt to the gastrointestinal tract of a human for the treatment or management of a condition,
wherein the method comprises: (a) admitting orally into the human a modified release dosage
25 form comprising a core and a membrane surrounding said core, said core comprising the
bupropion hydrobromide salt, a means for increasing the hydrostatic pressure within the core
and optionally a means for forcibly dispensing the bupropion hydrobromide salt from the
device, said membrane comprising at least one means for the exit ofthe bupropion
hydrobromide salt from the dosage form, and (b) administering the bupropion hydrobromide
30 salt from the dosage, form which is formulated such that when the dosage form is in an
aqueous medium, the bupropion hydrobromide salt, the means for increasing the hydrostatic pressure within the core and optionally the means for forcibly dispensing the bupropion hydrobromide salt and the at least one means for the exit ofthe bupropion hydrobromide salt

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cooperatively function to exhibit an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight of
the bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro
release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more
than about 40% is released, after about 4 hours from about 40% to about 75% is released,
after about 8 hours at least about 75% is released and after about 16 hours at least about 85%
10 is released.

SInat least one other embodiment, the osmotic dosage form further comprises an immediate release coat for the immediate release ofthe bupropion hydrobromide salt from the
immediate release coat. In embodiments comprising the immediate release coat, the osmotic
15 dosage form exhibits -vitro release rate such that alter about 2 hours from about 0% to
about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours
from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after
about 8 hours, from about 40% to about 90% by weight ofthe bupropion hydrobromide salt
is released, and after about 16 hours, more than about 80% by weight ofthe bupropion
20 hydrobromide salt is released. In at least one such embodiment the in-vitro release profile of
the bupropion hydrobromide salt is such that after about 2 hours no more than about 40 % is released, after about 4 hours from about 40% to about 75% is released, after about 8 hours at least about 75% is released and after about 16 hours at least about 85% is released.

25 In at least one other embodiment, the osmotic dosage forms further comprise an inert water-
soluble coat covering the semipermeable membrane or coat. This inert water-soluble coat
can be impermeable in a first external fluid, while being soluble in a second external fluid. In embodiments comprising the inert water-soluble coat, the osmotic dosage form exhibits an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight of
30 the bupropion hydrobromide salt is released, after about 4 hours from about 15% to about
45% by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from
about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is

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released. In at least one such embodiment the in-vitro release profile ofthe bupropion hydrobromide salt is such that after about 2 hours no more than about 40% is released, after about 4 hours from about 40% to about 75% is released, after about 8 hours at least about
75% is released and after about 16 hours at least about 85% is released.

In at least one other embodiment, the osmotic dosage forms further comprise an osmotic
subcoat. In certain embodiments comprising the osmotic subcoat, the osmotic dosage form exhibits an in-vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide salt is released, after about 4 hours from about 15% to
10 about 45% by weight of the bupropion hydrobromide salt is released, after about 8 hours,
from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is released. In at least one such embodiment the in-vitro release profile of the bupropion hydrobromide salt is such that after about 2 hours no more than about 40% is released, after
15 about 4 hours from about 40% to about 75% is released, after about 8 hours at least about
75% is released and after about 16 hours at least about 85% is released.

In at least one other embodiment, the osmotic dosage forms further comprise a controlled
release coat. The controlled release coat ofthe osmotic dosage form can, for example,
20 control, extend, and/or delay the release ofthe bupropion hydrobromide salt. In certain
embodiments comprising the controlled release coat, the osmotic dosage form exhibits an in-
vitro release rate such that after about 2 hours from about 0% to about 20% by weight ofthe
. bupropion hydrobromide salt is released, after about 4 hours from about 15% to about 45%
by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about
25 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about
16 hours, more than about 80% by weight ofthe bupropion hydrobromide salt is released. In
at least one such embodiment the in -vitro release profile ofthe bupropion hydrobromide salt
is such that after about 2 hours no more than about 40% is released, after about 4 hours from
about 40% to about 75% is released, after about 8 hours at least about 75% is released and
30 after about 16 hours at least about 85% is released.

In at least one embodiment, the controlled release coat ofthe osmotic dosage form comprises
a material that is soluble or erodible in intestinal juices, substantially pH neutral or basic

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fluids offluids having a pH higher than gastric fluid, but for the most part insoluble in gastric juices or acidic fluids.

In at least one embodiment, the controlled release coat ofthe osmotic dosage form comprises
at least one water-insoluble water-permeable film-forming polymer and at least one water-
soluble polymer.

In at least one embodiment, the controlled release coat of the osmotic dosage form comprises
at least one water-insoluble water-permeable film-forming polymer and at least one water-
10 soluble polymer and optionally at least one plasticizer.

SInat least one embodiment, the controlled release coat ofthe osmotic dosage form comprises at least one water-insoluble water-permeable film-forming polymer, at least one water-
soluble polymer and at least one means for the exit ofthe bupropion hydrobromide salt from
15 the core oftho osmotic dosage fonm

1I]

In at least one embodiment, the controlled release coat ofthe osmotic dosage form comprises
at least one water-insoluble water-permeable film-forming polymer, at least one water-
soluble polymer and at least one passageway.

In at least one embodiment, the controlled release coat ofthe osmotic dosage form comprises
at least one water-insoluble water-perrnable film-forming polymer, at least one water-
soluble polymer and at least one plasticizer.

25 In at least one embodiment, the controlled release coat ofthe osmotic dosage form comprises
at least one water-insoluble water-permeable film-forming polymer, at least one water-
soluble polymer, optionally at least one plasticizer, and at least one means for the exit of the bupropion hydrobromide salt from the core ofthe osmotic dosage form.

30 In at least one,embodiment, the controlled release coat ofthe osmotic dosage form comprises
at least one water-insoluble water-permeable film-forming polymer, at least one water-
soluble polymer, optionally at least one plasticizer, and at least one passageway.

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In at least one embodiment, the controlled release coat ofthe osmotic dosage form comprises
an aqueous dispersion of a neutral ester copolymer without any functional groups; a poly
glycol having a melting point greater than about 55°C, one or more pharmaceutically
acceptable excipients, and optionally at least one means for the exit ofthe bupropion hydrobromide salt form the core of the osmotic dosage form. This controlled release coat is cured at a temperature at least equal to or greater than the melting point ofthe polyglycol.

In at least one other embodiment, the controlled release coat ofthe osmotic dosage form comprises at least one enteric polymer.

In certain embodiments the membrane or wall is permeable to the passage of aqueous media
but not to the passage of the bupropion hydrobromide salt present in the core. The membrane can be, for example, a semipermeable membrane or an asymmetric membrane, which can be permeable, semipermeable, perforated, or unperforated and can deliver the bupropion
15 hydrobromide salt by osmotic pumping, or the combined mechanisms of diffusion and

20

osmotic pumping. The structural integrity ofsuch membranes preferably remain
substantially intact during the period of delivery of the bupropion hydrobromide salt. By
"substantially intact" it is meant that the semipermeable property ofthe membrane is not compromised.during the period of delivery ofthe bupropion hydrobromide salt.

The semipermeable membrane ofthe osmotic dosage form of certain embodiments comprises
at least one pharmaceutically acceptable excipient, at least one polymer, wax, or combination
. thereof, although appropriately treated inorganic materials such as ceramics, metals or glasses
can be used. When the semipermeable membrane comprises at least one polymer, the
25 molecular weight of the at least one polymer or combination ofpolymers are preferably such
that the polymer or combination ofpolymers is solid at the temperature of use i.e., both in-
vitro and in-vivo.

In certain embodiments, the at least one polymer included in the semipermeable membrane of
30 the osmotic dosage form can be a cellulose ester, such as for example, cellulose acetate,
cellulose acetate acetoaeetate, cellulose acetate benzoate, cellulose acetate butylsulfonate, cellulose acetate butyrate, cellulose acetate butyrate sulfate, cellulose acetate butyrate
valerate. cellulose acetate eaprafe, cellulose acetate caproate, cellulose acetate caprylate,

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cellulose acetate carboxymethoxypropionate, cellulose acetate chioroacetate, cellulose acetate dimethaminoacetate, cellulose acetate dimethylaminoacetate, cellulose acetate
dimethylsulfamate, cellulose acetate dipalmitate, cellulose acetate dipropylsulfamate,
cellulose acetate ethoxyacetate, cellulose acetate ethyl caibamate, cellulose acetate ethyl
5 carbonate, cellulose acetate ethyl oxalate. cellulose acetate furoate, cellulose acetate
heptanoate, cellulose acetate heptylate, cellulose acetate isobutyrate, cellulose acetate laurate, cellulose acetate methacrylate, cellulose acetate methoxyacetate, cellulose acetate methylcarbamate, cellulose acetate methylsulfonate, cellulose acetate myristate, cellulose
acetate octanoate, cellulose acetate palmitate, cellulose acetate phthalate, cellulose acetate
10 propionate, cellulose acetate propionate sulfate, cellulose acetate propionate valerate,
cellulose acetate p-toluene sulfonate, cellulose acetate succinate, cellulose acetate sulfate, cellulose acetate trimellitate, cellulose acetate tripropionate, cellulose acetate valerate,
cellulose benzoate, cellulose butyrate napthylate, cellulose butyrate, cellulose chlorobenzoate, cellulose cyanoacetates, cellulose dicaprylate, cellulose dioctanoate, cellulose dipentanate,
15 cellulose dipentaniate, cellulose formate, cellulose methacrylats, cellulose methoxybenzoate,
cellulose nitrate, cellulose nitrobeuzoate, cellulose phosphate (sodium salt), cellulose phosphinates, cellulose phosphites, cellulose phosphonates, cellulose propionate, cellulose propionate crotonate, cellulose propionate isobutyrate, cellulose propionate succinate,
cellulose stearate, cellulose sulfate (sodium salt), cellulose triacetate, cellulose tricaprylate,
20 cellulose triformate, cellulose triheptanoate, cellulose triheptylate, cellulose trilaurate,
cellulose trimyristate, cellulose trinitrate, cellulose trioctano ate, cellulose tripalmitate,
cellulose tripropionate, cellulose trisuccinate, cellulose trivalerate, cellulose valerate
palinitate; a cellulose ether, such as for example, 2-cyanoethyl cellulose, 2-hydroxybutyl
methyl cellulose, 2-hydroxyethyl cellulose, 2-hydroxyethyl ethyl cellulose, 2-hydroxyethyl
5 methyl cellulose, 2-hydroxypropyl cellulose, 2-hydroxypropyl methyl cellulose,
dimetboxyethyl cellulose acetate, ethyl 2-hydroxylethyl cellulose, ethyl cellulose, ethyl
cellulose sulfate, ethylcellulose dirnethylsuifamate, methyl cellulose, methyl cellulose
acetate, methyl.cyanoethyl cellulose, sodium carboxymethyl 2-hydroxyethyl cellulose, sodium carboxymethyl cellulose; a polysulfone, such as for example, polyethersulfones; a
30 polycarbonate; a polyurethane; a polyvinyl acetate; a polyvinyl alcohol; a polyester; a
polyalkene such as polyethylene, efhylene vinyl alcohol copolymer, polypropylene, poly(l,2-dimethyl.- 1 -butenylene), poly(1 -brorno- 1 -butenylene), poly(i, butene), poly(i-chloro- 1 butenylene), poly(l -decyl- 1 -butenylene), poly(l-hexane), poly(l-isopropyl- 1 -butenylene),

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poly(1 -pentene), poly(3 -viny1pyrene, poly(4-methoxyl 1 -butenylene), po!y(ethylene-co-methyl styrene, poly vinyl-chloride, poly(ethylone-co-tetrafluoroethylene), poly(ethylene-terephthalate), poly(dodecafluorobutoxylethylene),
0 ly(hexafluoroprolylcne), 0 ly(hexyloxyethylene), poly(isobutene), 0 iy(isobutene-co-isoprene), poly(isopicne), poly-butadiene, poly[pcntafluoroethyl)ethylene], poly[2-cthylhexyloxy)ethylene], poly(butylethylene), poly(tertbutylethylene), poly(cyiclohexylethy-lene), poly[(cyclohcxylmethyl)ethylene], poly(eyelopentylethylene), poly(decylcthylene), pot y-(dodecy-lethylene), poly(neopentylethyleue), poly(propylethylene); a polystyrene, such as
for example, poly(2,4-dimethyl styrene), poly(3-methyl styrene), poly(4-methoxystyiene),
10 poly(4-methoxystyrene-stat-styrene), poly(4-methyl styrene), poly(isopentyl styrene),
poly(isopropyl styrene), polyvinyl esters or polyvinyl ethers, such as form example, poly(benzoylethylene), poly(butoxyethylene), poly(ehloroprene),
poly(cyclohexloxyethylene), poly(decyloxyethylene), poly(dichloroethylene), poly(difluoroethylene), poly(vinyl acetate), poly(vinyltrimethyilstyrene); a polysiloxane, such
15 as for example, poly(climethylsiloxane); a polyacrylic acid derivative, such as for example,
polyacrylates, polyrnethyl methacrylate, poly(acrylic acid) higher alkyl esters, poly(ethylmethacrylate), poly(hexadecyi methacrylate-co-methyhnethacrylate), poly-(methylaciylate-co-styrene), poly(n-butyl methacrylate), poly(n-.butyl-acrylate), poly (cyclododecyl acrylate), poly(benzyl acrylate), poly(butylacrylate), poly(secbutylacrylate),
20 poly(hexyl acrylate), poly(octyl acrylate), poly(decyl acrylate), poly(dodecyl acrylate),
poly(2-methyl butyl acrylate), poly(adamantyl methacrylate), poly(benzyl methacrylate), poly(butyl methacrylate), poly(2-ethylhexyl methacrylate), poly(octyl methacrylate), acrylic resins; a polyamide, such as for example, poly(irninoadipoyliminododecamethylene), poly(iminoadipoyliminohexamethylene), polyethers, such as for example,
25 poly(o ctyloxyethylene), poly(oxyphenylethylene), poly(oxypropyiene),
poly(pentyloxyethylene), poly(phenoxy styrene), poly(secbutroxylethylene), poly(tert-butoxyethylene); and combinations thereof.

In at least one embodiment, the at least one wax included in the semipermeable membrane of
30 the osmotic dosage form can be, for example, insect and animal waxes, such as for example,
chinese insect wax, beeswax, spermaceti, fats and wool wax; vegetable waxes, such as for example, bamboo leaf wax, candelilla wax, carnauba wax, Japan wax, ouricury wax, Jojoba
wax, bayberry wax, Douglas-Fir wax, cotton wax, cranberry wax, cape berry wax, rice-bran

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wax, castor wax, indian corn wax, hydrogenated vegetable oils (e.g., castor, palm, cottonseed, soybean), sorghum grain wax, Spanish moss wax, sugarcane wax, caranda wax, bleached
wax, Esparto wax, flax wax, Madagascar wax, orange peel wax, shellac wax, sisal hemp wax
and rice wax; mineral waxes, such as for example, Montan wax, peat waxes, petroleum wax,
5 petroleum ocresin, ozokerite wax, microcrystalline wax and paraffins; synthetic waxes, such
as for example, polyethylene wax, Fischer-Tropsch wax, chemically modified hydrocarbon
waxes, cetyl esters wax; and combinations thereof

In at least one embodiment, the semipermeable membrane of the osmotic dosage form can
10 comprise a combination of at least one polymer, wax, or combinations thereof and optionally
at least one excipient.

In embodiments where the bupropion hydrobromide salt is released through the membrane or wall in a controlled mariner by the combined mechanisms of diffusion and osmotic pumping,
15 the membrane or wall can comprise at least one ofthe above described polymers and/or
waxes or a combination ofpolymers, such as for example, cellulose esters, copolymers of methacrylate salts and optionally a plasticizer.

The poly(methacrylate) copolymer salts used in the manufacturing ofthe membrane for the
20 osmotic dosage form can be, for example, insoluble in water and in digestive fluids, but are
permeable to different degrees. Examples of such copolymers are poly(arnmomium methacrylate) copolymer RL (EUDRAGITfiRL), poly(arnmonium methacrylate) copolymer (type A-USP/NF), poly(aminoallcyl methacrylate) copolymer RL-JSP I), and (ethyl. acrylate)- (methyl methacrylate)-[trimethylammoniun)-ethylmethacrylate] (1:2:0,2) copolymer, MW
25 150,000. Other examples ofsuch copolymers include EUDRAGITfiRS 100: solid polymer,
EUDRAGITfiRL 12.5:12.5% solution in solvent, EUDRAGITfiRL 30 D: 30% aqueous dispersion, and other equivalent products. The following poly (ammonium methacrylate) copolymers can also be used: ammonium methacrylate copolymer RS (EUDRAGITfiRS), poly(ammonium methacrylate) copolymer (type B-USP/NF), poly(aminoallcyl methacrylate)
30 copolymer (RSL-JSP I), (ethyl acrylate)-(methyl methaciylate)-[(trimethylammonium-ethyl
methacrylate] (1:2:0.1) copolymer, PM 150,000. Specific polymers include:
EUDRAGITfiRS 100: solid polymer, EUDRAGITfiRS 12.5: 12.5% solution in solvent, EUDRAGITfiRS 30 D: 30% aqueous dispersion and other equivalent products. RL is

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readily water permeable while ETJDRAGITfiRS is hardly water permeable. By employing mixtures ofboth EUDRAGITfiRL and EIJDRAGITfiRS, membranes having the desired degree ofpermeability to achieve the in-vitro dissolution rates and in-vivo pharmacokinetic parameters can be prepared.

The use ofplasticizers is optional but can be included in the osmotic dosage forms of certain embodiments to modify the properties and characteristics ofthe polymers used in the coats or core ofthe osmotic dosage forms for convenient processing during manufacture ofthe coats and/or the core ofthe osmotic dosage forms if necessary. As used herein, the term 10"plasticizer" includes any compounds capable of plasticizing or softening a polymer or binder used in invention. Once the coat or membrane has been manufactured, certain plasticizers
can function to increase the hydrophilicity ofthe coat(s) and/or the core ofthe osmotic
dosage form in the environment ofuse. During manufacture ofthe coat, the plasticizer
lowers the melting temperature or glass transition temperature (softening point temperature)
15 ofthe polymer or binder. Plasticizers, such as low molecular weight PEG, can be included
with a polymer and lower its glass transition temperature or softening point. Plasticizers also can reduce the viscosity of a polymer. The plasticizer can impart some particularly advantageous physical properties to the osmotic device of the invention.

20 Plasticizers useful in the osmotic dosage form of certain embodiments ofthe invention can
include, for example, low molecular weight polymers, oligomers, copolymers, oils, small
organic molecules, low molecular weight poiyols having aliphatic hydroxyls, ester-type plasticizers, glycol ethers, poly(propylene glycol), multi-block polymers, single block
polymers, low molecular weight poly(ethylene glycol), citrate ester-type plasticizers,
25 triacetin, propylene glycol, glycerin, ethylene glycol, 1,2-butylene glycol, 2,3-butylene
glycol, styrene glycol, diethylen.e glycol, triethylene glycol, tetraethylene glycol and other poly(ethylene glycol) compounds, monopropylene glycol monoisopropyl ether, propylene glycol monoethyl ether, ethylene glycol monoethyl ether, diethylene glycol monoethyl ether, sorbitol lactate, ethyl lactate, butyl lactate, ethyl glycolate, dibutylsebacate,
30 acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate, allyl glycolate and
mixtures thereof. It is also contemplated and within the scope ofthe invention, that a combination of plasticizers can be used in the present formulation. The PEG based
plasticizers are available commercially or can be made by a variety ofmethods, such as

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disclosed in Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications (J.
M. Harris, Ed.; Plenum Press, NY). Once the osmotic dosage form is manufactured, certain plasticizers can function to increase the hydrophilicily ofthe coat(s) and/or the core ofthe osmotic dosage form in the environment of use may it be in-vitro or in-vivo. Accordingly,
5 certain plasticizers can function as flux enhancers.

The ratio of cellulose esters:copolymers ofmethacrylate salts:plasticizer ofthe osmotic
dosage forms can be, for example, about 1% to about 99% of the cellulose ester by weight: about 05% to about 84% ofthe copolymers ofmethacrylate salt by weight: about 0.5% to’
10 about 15% ofthe plasticizer by weight including all values and ranges therebetween. The
total weight percent of all components comprising the wall is 100%.

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Aside from the semipermeable membranes ofthe osmotic dosage form described above, asymmetric membranes can also be used to surround the core of an osmotic dosage form for
15 the controlled release ofthe bupropion hydrobromide salt to provide the in-vitro release rates
described above and the therapeutically beneficial in-vivo pharmacokinetic parameters for the treatment or management of a condition. Such asymmetric membranes can be permeable, semipermeable, perforated, or unperforated and can deliver the bupropion hydrobromide salt
by osmotic pumping, diffusion or the combined mechanisms of diffusion and osmotic
20 pumping. The manufacture and use thereof of asymmetric membranes for the controlled-
release of an active drug through one or more asymmetric membranes by osmosis or by a combination of diffusion osmotic pumping is known.

In certain embodiments ofthe osmotic dosage form, the semipermeable membrane can
25 further comprise a flux enhancing, or channeling agent. "Flux enhancing agents" or
"channeling agents" are any materials which function to increase the volume offluid imbibed
into the core to enable the osmotic dosage form to dispense substantially all of the bupropion hydrobromide salt through at least one passageway in the semipermeable membrane by
osmosis or by osmosis and by diffusion through the semipermeable membrane. The flux
30 enhancing agent dissolves to form paths in the semipermeable membrane for the fluid to enter
the core and dissolve the bupropion hydrobromide salt in the core together with the
osmagent, if one is present, but does not allow exit ofthe bupropion hydrobromide salt. The
flux enhancing agent can be any water soluble material or an enteric material which allows an

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increase in the volume of liquid imbibed into the core but does not allow for the exit ofthe bupropion hydrobromide salt. Such materials can be, for example, sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl nethy1cc1lulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic copolymers, and combinations thereof. Some plasticizers can also function as flux enhancers by increasing the hydrophilicity of the semipermeable membrane and/or the core ofthe osmotic dosage form..
Flux enhancers or channeling agents can also function as a means for the exit ofthe
bupropion hydrobromide salt from the core ifthe flux enhancing or channeling agent is used
10 in a sufficient amount.

The expression "passageway" as used herein comprises means and methods suitable for the metered release ofthe bupropion hydrobromide salt from the core ofthe osmotic dosage
form. The means for the exit of the bupropion hydrobromide salt comprises at least one
15 passageway, including orifice, bore, aperture, pore, porous element, hollow fiber, capillary
tube, porous overlay, or porous element that provides for the osmotic controlled release ofthe bupropion hydrobromide salt. The means for the exit can be linear or tortuous. The means
for the exit includes a weakened area ofthe semipermeable membrane or a material that
erodes or is leached from the wall in a fluid environment of use to produce at least one
20 dimensioned passageway. The means for the exit ofthe bupropion hydrobromide salt can
comprise any leachable material, which when leaches out ofthe semipermeable membrane
forms a passageway suitable for the exit ofthe bupropion hydrobromide salt from the core of
the osmotic dosage form. Such leachable materials can comprise, for example, a leachable poly(glycolic) acid or poly(lactic) acid polymer in the semipermeable membrane, a gelatinous
25 filament, poly(vinyl alcohol), leachable polysaccharides, salts, oxides, sorbitol, sucrose or
mixtures thereof. The means for exit can also comprise a flux enhancer or channeling agent
if present in a sufficient amount. The means for the exit possesses controlled-release
dimensions, such as round, triangular, square and elliptical, for the metered release ofthe bupropion hydrobromide salt from the dosage form. The dimensions ofthe means ofthe exit
30 for the bupropion hydrobromide salt is sized such so as to allow the bupropion hydrobromide
salt to pass through the means for the exit. The dosage form can be constructed with one or more means for the exit in spaced apart relationship on a single surface or on more than one surface ofthe wall.

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The expression "fluid environment" denotes an aqueous or biological fluid as in a human
patient, including the gastrointestinal tract. The means for the exit can be preformed for example by mechanical means after the semipermeable membrane is applied to the core of
5 the osmotic dosage form, such as for example by mechanical perforation, laser perforation, or
by using a properly sized projection on the interior of a tablet punch to form the means for the
exit ofthe bupropion hydrobromide salt, such as for example a cylindrical or frustoconical
pin which is integral with the inside surface ofthe upper punch of a punch used to form the
osmotic dosage form. Alternatively, the means for the exit ofthe bupropion hydrobromide
10 salt can be formed by incorporating a leachable material or pore forming agent into the
semipermeable composition before the semipermeable membrane is applied to the core of the Iosmotic dosage form. The means for the exit ofthe bupropion hydrobromide salt can comprise a combination of the different exit means described above. The osmotic dosage
form can comprise more than one means for the exit ofthe bupropion hydrobromide salt
15 including two, three, four, five, six seven, eight, nine ten or more exit means and can be
formed in any place ofthe osmotic dosage form. The various positions ofthe means for the
exit are disclosed. The type, number, and dimension(s) ofthe means for the exit ofthe
bupropion hydrobromide salt is such that the dosage form exhibits the desired in-vitro release rates described herein and can be determined by routine experimentation by those skilled in
20 the pharmaceutical delivery arts. The means for the exit and equipment for forming the
means for the exit are lunown.

The osmotic device can further comprise a controlled release coat surrounding the semipermeable membrane comprising an enteric or delayed release coat that is soluble or
25 erodible in intestinal juices, substantially pH neutral or basic fluids of fluids having a pH
higher than gastric fluid, but for the most part insoluble in gastric juices or acidic fluids. A
wide variety of other polymeric materials are known to possess these various solubility properties. Such other polymeric materials include, for example, cellulose acetate phthalate (CAP), cellulose acetate trimelletate (CAT), poly(vinyl acetate) phthalate (PVAP),
30 hydroxypropyl methylcellulose phthalate HP), poly(n ethacrylate ethylacrylate) (1:1)
copolymer (MA-EA), poly(methacrylate methylmethacrylate) (1:1) copolymer (MA-MMA), poly(mcthacrylate methylmethacrylate) (1:2) copolymer, EUDRAGITfi L-3 0-D (MA-EA,
1:1), EUDRAGITfi L- 100-55 (MA-EA, 1:1), hyciroxypropyl methylcellulose acetate

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succinate (HPMCAS), COATERICfi (PVAP), AQUATERICfi (CAP), AQUACOATfi (HPMCAS) and combinations thereof. The enteric coat can also comprise dissolution aids, stability modifiers, and bioabsorption enhancers.

In at least one embodiment the controlled release coat of certain osmotic dosage forms
include materials such as hydroxypropylcellulose, microcrystalline cellulose (e.g. MCC, AVICELTM), poly (ethylene-vinyl acetate) (60:40) copolymer (EVAC), 2-hydroxyethylmethacrylate (HEMA), MMA, terpolymers ofHEMA: MMA:MA synthesized
in the presence ofN,N-bis(methacryloyloxyethyloxycarbonylamino)-azobenzene,
10 azopolymers, enteric coated timed release system (TIME CLOCKfi), calcium pectinate, and
mixtures thereof.

Polymers that can be used in the controlled release coat of osmotic dosage forms of certain embodiments can be, for example, enteric materials that resist the action of gastric fluid
15 avoiding permeation through the semipermeable wail while one or more ofthe materials in
the core ofthe dosage form are solubilized in the intestinal tract thereby allowing delivery of
the bupropion hydrobromide salt in the core by osmotic pumping in the osmotic dosage form
to begin. A material that adapts to this kind ofrequirement can be, for example, a poly(vinylpyrrolidone)-vinyl acetate copolymer (e.g. KOLLIDONfi VA64), mixed with
20 magnesium stearate and other similar excipients. The coat can also comprise povidone (e.g.
KOLLIDONfi K 30), and hydroxypropyl methylcellulose (e.g. METHOCELfi E-15). The materials can be prepared in solutions having different concentrations ofpolymer according
to the desired solution viscosity. For example, a 10% P/V aqueous solution of KOLLIDONfi
K. 30 has a viscosity of about 5.5 to about 8.5 cps at 20°C, and a 2% P/V aqueous solution of
25 METHOCELfi E-15 has a viscosity of about 13 to about 18 cps at 20°C,

The controlled release coat of osmotic dosage forms of certain embodiments can comprise
one or more materials that do not dissolve, disintegrate, or change their structural integrity in
the stomach and during the period oftime that the tablet resides in the stomach, such as for
30 example a member chosen from the group (a) keratin, keratin saridarac-tolu, salol (phenyl
salicylate), salol beta-naphthylbenzoate and acetotamiin, salol with balsam of Peru, salol with tolu, salol with gum mastic, salol and stearic acid, and salol and shellac; (b) a member chosen from the group offormalized protein, formalized gelatin, and formalized cross-linked gelatin

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and exchange resins; (c) a member chosen from the group ofmyristic acid-hydrogenated castor oil-cholesterol, stearic acid-mutton tallow, stearic acid-balsam oftolu, and stearic acid-castor oil; (d) a member chosen from the group ofshellac, ammoniated shellac, ammoniated shellac-salol, shellac-wool fat, shellac-acetyl alcohol, shellac-stearic acid-balsam oftolu, and shellac n-butyl stearate; (e) a member chosen from the group of abietic acid, methyl abictate, benzoin, balsam oftolu, sandarac, mastic with tolu, and mastic with tolu, and mastic with
acetyl alcohol; (I) acrylic resins represented by anionic polymers synthesized from
methacrylate acid and methacrylic acid methyl ester, copoiymeHc acrylic resins of
methacrylic and methacrylic acid and methacrylic acid alkyl esters, copolymers of alkacrylic
10 acid and alkacrylic acid alkyl esters, acrylic resins such as dimethylaminoethylinethacrylate-
butylmethacrylate-methylmethacrylate copolymer of about 150,000 molecular weight,

40 methacrylic acid-methylmethacrylate 50:50 copolymer of about 135,000 molecular weight,
methacrylic acid-niethylmethacrylate-3 0:70 -copolymer of about 135,000 mot. wt.,
methacrylic acid-dimethylarriino ethyl-methacxyylate-ethylacrylate of about 750,000 mot. wt.,
15 methacrylic acid-methylmethacrylate-ethylacrylate of about 1,000,000 mol, wt., and
ethylacrylate-methylmethacrylate-ethylaerylate of about 550,000 mot. wt; and, (g) an enteric composition chosen from the group of cellulose acetyl phthalate, cellulose diacetyl phthalate,
cellulose triacetyl phthalate, cellulose acetate phthalate, hydroxypropyl methylcellulose
phthalate, sodium cellulose acetate phthalate, cellulose ester phthalate, cellulose ether
20 phthalate, methylceliulose phthalate, cellulose ester-ether phthalate, hydroxypropyl cellulose
phthalate, alkali salts of cellulose acetate phthalate, alkaline earth salts of cellulose acetate phthalate, calcium salt of cellulose acetate phthalate, ammonium salt of hydroxypropyl methylceilniose phthalate, cellulose acetate hcxahydrophthalate, hydroxypropyl
methylcellulose hexahydrophthalate, polyvinyl acetate phthalate diethyl phthalate, dibutyl
25 phthalate, dialkyl phthalate wherein the ailcyl comprises from about I to about 7 straight and
branched alkyl groups, aryl phthalates, and other materials known to one or ordinary skill in
the art. Combinations thereof are operable.

Accordingly, in at least one othef embodiment, the controlled release coat of osmotic dosage
30 forms of certain embodiments comprises a water-insoluble water-permeable film-forming
polymer, water-soluble polymer, and optionally a plasticizer and/or a pore-forming agent.
The water-insolubic, water-permeable film-forming polymers useful for the manufacture of
the controlled release coat can be cellulose ethers, such as for example, ethyl celiuloses

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chosen from the group of ethyl cellulose grade PR100, ethyl cellulose grade PR20, cellulose esters, polyvinyl alcohol, and any combination thereof. The water-soluble polymers useful for the controlled release coat can be, for example, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, and any combination thereof,

The skilled artisan will appreciate that that the desired in-vitro release rates described herein
for the bupropion hydrobromide salt can be achieved by controlling the permeability and/or
the amount of coating applied to the core ofthe osmotic dosage form. The permeability of
the controlled release coat, can be altered by varying the ratio ofthe water-insoluble, water-
10 permeable film-forming polymer:water-soluble polymer: optionally the plasticizer and/or the
quantity of coating applied to the core ofthe osmotic dosage form. A more extended release
is generally obtained with a higher amount ofwater-insoluble, water-permeable film forming polymer. The addition of other excipients to the core ofthe osmotic dosage form can, also
alter the permeability ofthe controlled release coat. For example, ifthe core ofthe osmotic
15 dosage form comprises a swellable polymer, the amount of plasticizer in the controlled
release coat can be increased to make the coat more pliable as the pressure exerted on a less pliable coat by the swellable polymer could rupture the coat. Further, the proportion ofthe water-insoluble water-permeable film forming polymer and water-soluble polymer can also
be altered depending on.whether a faster or slower in-vitro dissolution is desired.
20

In at least one other embodiment, the controlled release coat ofthe osmotic dosage form comprises an aqueous dispersion of a neutral ester copolymer without any functional groups;
a poly glycol having a melting point greater than about 55°C, and one or more
pharmaceutically acceptable excipidnts and cured at a temperature at least equal to or greater
25 than the melting point ofthe poly glycol. The manufacture and use ofsuch coating
formulations are known. In brief, examples of neutral ester copolymers without any
functional groups comprising the coat can be EUDRAGITfi NE30D, EUDRAGITfi NE401),
or mixtures thereof. This Coat can comprise hydrophilic agents to promote wetting ofthe
coat when in contact with gastrointestinal fluids. Such hydrophilic agents include, for
30 example, hydrophilic water-soluble polymers such as,hydroxypropyl methylceliulose
(HPMC), hydroxypropyl cellulose (HPC) and combinations thereof. The poly glycol can be,
for example, chosen from the group ofpolyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 20000, Poloxamer 188, Poloxamer 338,

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Poloxamer 407, Polyethylene Oxides, Polyoxyethylene Alkyl Ethers, and Polyoxyethylene Stearates, and combinations thereof. This controlled release coat of the osmotic dosage form can further comprise a pore-forming agent. In at least one embodiment the pore former is sufficiently insoluble in the aqueous dispersion, and is sufficiently soluble in the environment
5 ofuse. Methods for producing such coats are known.

The controlled release coat of certain embodiments ofthe osmotic dosage form of certain embodiments ofthe present invention includes at least one polymer in an amount sufficient to achieve a controlled release ofthe bupropion hydrobromide salt. Examples of polymers that
10 can be used in the controlled release coat ofthese embodiments include cellulose acetate
phthalate, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, ammonio methacrylate copolymers such as EUDRAGITfi RS and RL, poly acrylic acid and poly acrylate and methacrylate copolymers such as EUDRAGITfi S and L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate,
15 shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium
alginate, sodium carmellose, calcium carmeilose, sodium carboxymethyl starch, poly vinyl
alcohol, hydroxyethyl cellulose, methyl cellulose, gelatin, starch, and cellulose based cross-
linked polymers in which the degree of crosslinking is low so as to facilitate adsorption of
water and expansion of the polymer matrix, hydroxypropyl cellulose, hydroxypropyl
20 methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin,
aminoacryl-methacrylate copolymer (e.g. EUD’RAGITfi RS-PM), pullulan, collagen, casein,
agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (molecular weight from about 5K to about 5000K), polyvinylpyrrolidone (molecular weight from about 10K to about 360K), anionic and cationic
25 hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and
carboxymethyl cellulose, copolymers ofmaleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (molecular weight from about 30K to about 3001-C), polysaccharides such
as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, POLYOXfi
polyethylene oxides (molecular weight from about 100K to about 5000K, AQUAKEEPfi
30 acrylate polymers, diesters ofpolyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-
pyrrolidone, sodium starch glycolate (e.g. EXPLOTABfi); hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose,
hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro

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cellulose, carboxyniethyl cellulose, cellulose ethers, polyethylene oxides (e.g. POLYOX), methyl ethyl cellulose, ethylliydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, collagen, starch, maltodextrin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic
acid, copolymers ofmethacrylic acid or methacrylic acid (e.g. EUDRAGITfi), other acrylic
acid derivatives, sorbitan esters, natural gums, lecithins, pectin, alginates, ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, and gums such as
arabic, karaya, locust bean, tragacanth, carrageens, guar, xanthan, scieroglucan and mixtures
and blends thereof. In at least one embodiment ofthe osmotic dosage form ofthe present
10 invention, the polymer is an acrylate dispersion such as EUDRAGITfi NE30D,
EUDRAGITfi NE40D, KOLLICOATfi SR 30D, SURELEASEfi, or a mixture thereof. The polymer can be present in an amount of from about 20% to about 90% by weight ofthe controlled release coat including all values and ranges therebetween, depending on the
controlled release profile desired. For example, in certain embodiments ofthe osmotic
15 dosage form, the polymer is present in an amount offrom about 50% to about 95%, in other
embodiments from about 60% to about 90%, and in still other embodiments about 75% ofthe
controlled release coat weight.

The controlled release coat of certain embodiments ofthe osmotic dosage form ofthe present
20 invention can also include one or more pharmaceutically acceptable excipients such as
lubricants, emulsifiers, anti-foaming agents, plasticisers, solvents and the like.

’ Lubricants can be included in the controlled release coat of certain embodiments ofthe
osmotic dosage form ofthe present invention to help reduce friction of coated microparticles
25 during manufacturing. The lubricants that can be used in the controlled release coat include
but are not limited to adipic acid, magnesium stearate, calcium stearate, zinc stearate, calcium
silicate, magnesium silicate, hydrogenated vegetable oils, sodium chloride, sterotex,
polyoxyethylene, glyceryl monostearate, talc, polyethylene glycol, sodium benzoate, sodium
lauryl sulfate, magnesium lauryl sulfate, sodium stearyl furnarate, light mineral oil, waxy
30 fatty acid esters such as glyceryl behenate, (i.e. COMPRTTOLTM), STEAROWETTM and
MYVATEXTM TL. Combinations ofthese lubricants are operable. In at least one
embodiment, the lubricant is selected from magnesium stearate, talc and a mixture thereof
The lubricant(s) can each be present in an amount of from about 0.1% to about 80% ofthe

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controlled release coat weight including all values and ranges therebetween. For example, in certain embodiments the lubricant is present in an amount of from about 0.5% to about 20%, in other embodiments from about 0.8% to about 10%, and in still other embodiments about
1.5% ofthe controlled release coat weight.

Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the controlled release coat ofthe osmotic dosage forms of certain embodiments ofthe present invention to facilitate actual emulification during manufacture ofthe coat, and also to increase or ensure emulsion stability during the shelf-life ofthe product. Emulsifying agents useful for the
10 controlled release coat composition of the osmotic dosage form include, but are not limited to
naturally occurring materials and their semi synthetic derivatives, such as the
polysaccharides, as well as glycerol esters, cellulose ethers, sorbitan esters (e.g. sorbitan monooleate or SPANTM 80), and polysorbates (e.g. TWEENIM 80). Combinations of emulsifying agents are operable. The emulsifying agent(s) can be present in an amount of
15 from about 0.01% to about 0.25% ofthe controlled release coat weight including all values

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and ranges therebetween. For example, in certain embodiments the emulsifying agent is
present in an amount offrom about 0.01% to about 0.15%, in other embodiments from about 0.01% to about 0.07%, and in still other embodiments about 0.03% ofthe controlled release
coat weight.

Anti-foaming agent(s) can be included in the controlled release coat ofthe osmotic dosage
form of certain embodiments ofthe present invention to reduce frothing or foaming during manufacture of the coat. Anti-foaming agents useful for the controlled release coat
composition ofthe osmotic dosage form include, but are not hininted to sirnethicone,
25 polyglycol, silicon oil and mixtures thereof. In at least one embodiment the anti-foaming
agent is Simethicone C. The anti-foaming agent can be present in an amount of from about 0.01% to about 10% of the controlled release coat weight including all values and ranges therebetween. For certain embodiments the anti-foaming agent is present in an amount offrom about 0.05% to about 1%, in other embodiments from about 0.1% to about
30 0.3%, and in still other embodiments about 0.15% ofthe controlled release coat weight.

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It is contemplated that in certain embodiments, other excipients consistent with the objects of the present invention can also be used in the controlled release coat of the osmotic dosage
form.

In at least one embodiment, the controlled release coat ofthe osmotic dosage form includes
about 75% EUDRAGITfi NE30D, about 1,5% Magnesium stearate, about 1.5% Talc, about 0.03% TWEENTM 80, about 0.15% Simethicone C, and about 21.82% water, by weight ofthe controlled release coat composition.

10 The osmotic dosage form of certain embodiments can be made according to any one ofthe
methods described herein. In a prophetic example of certain embodiments of osmotic dosage forms ofthe present invention, the manufacturing process for the controlled release coat of
The osmotic dosage form can hypothetically be as follows: Water is split into two portions of about 15% and about 85%. The anti-foaming agent and the emulsifying agent are then added
15 to the 15% water portion, and mixed at about 300 rpm to form portion A. In at least one
embodiment, the anti-foaming agent is Simethicone C, and the emulsifying agent is
TWEENTM 80. A first lubricant is then added to the 85% water portion and mixed at about
9500 rpm to form portion B. In at least one embodiment, the first lubricant is talc. Then
portion A is mixed with portion B, a second lubricant is slowly added, and mixed at about
20 700 rpm overnight. In at least one embodiment, the second lubricant is magnesium stearate.
Finally, an aqueous dispersion of a neutral ester copolymer is added and mixed for about 30
minutes at about 500 rpm. In at least one embodiment, the aqueous dispersion of a neutral
. ester copolymer is EUDRAGITfi NE30D. The resultant coat solution can then be used to
coat the osmotic subcoated microparticles to about a 35% weight gain with the following
25 parameters: An inlet temperature of from about 10°C to about 60°C including all values and
ranges therebetween, in certain embodiments from about 20°C to about 40°C, and in at least
one embodiment from about 25°C to about 35°C; an outlet temperature offrom about 10°C to
about 60°C including all values and ranges therebetween, in certain embodiments from about
20°C to about 40°C, and in at least one embodiment from about 25°C to about 35°C; a product
30 temperature of from about 10°C to about 60°C including all values and ranges therebetween,
in certain embodiments from about 15°C to about 35°C, and in at least one embodiment from about 22°C to about 27°C; an air flow offrom about 10 cmlh to about 180 cmlh including all values and ranges therebetween, in certain embodiments from about 40 crnlh to about 120

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cm/h, and in at least one embodiment from about 60 em/h to about 80 cm/h; and an atomizing pressure of from about 0.5 bar to about 4.5 bar including all values and ranges therebetween,
in certain embodiments from about 1 bar to about 3 bar, and in at least one embodiment at
about 2 bar. The resultant coated microparticles can then be discharged from the coating
5 chamber and overcured with the following parameters: A curing temperature of from about
20°C to about 65°C including all values and ranges therebetween, in certain embodiments
from about 30°C to about 55°C, and in at least one embodiment at about 40°C; and a curing
time Of from about 2 hours to about 120 hours including all values and ranges therebetween,
in certain embodiments from about 10 hours to about 40 hours, and in at least one
10 embodiment at about 24 hours. Any other technology resulting in the coating formulation of
the controlled release coat ofthe osmotic dosage form that is consistent with the objects of
the invention can also be used.

In at least one other embodiment, the osmotic dosage forms comprise a water-soluble or
15 rapidly dissolving coat between the semipermeable membrane and the controlled release coat.
The rapidly dissolving coat can be soluble in the buccal cavity and/or upper GI tract, such as
the stomach, duodenum, jejunum or upper small intestines. Materials suitable for the manufacture ofthe water-soluble coat are known. In certain embodiments, the rapidly
dissolving coat can be soluble in saliva, gastric juices, or acidic fluids. Materials which are
20 suitable for making the water soluble coat or layer can comprise, for example, water soluble
polysaccharide gums such as carrageenan, fucoidan, gum ghatti, tragacanth, rabinogalaetan, pectin, and xanthan; water-soluble salts ofpolysaccharide gums such as sodium alginate,
sodium tragacanthin, and sodium gum ghattate; water-soluble hydroxyaJkylcellulose wherein
the athyl member is straight or branched of 1 to 7 carbons such as, for example,
25 hydroxymethylcellulose, hydroxyethyicellulose, and hydroxypropylcellulose; synthetic
water-soluble cellulose-based lamina formers such as, for example, methyl cellulose and its hydroxya&yl methylcellulose cellulose derivatives such as a member chosen from the group ofhydroxyethyl methyicellulose, hydroxpropyl methylceilulose, and hydroxybutyl methylcellulose; croscarmellose sodium; other cellulose polymers such as sodium
30 carboxymethylceilulose; and mixtures thereof. Other lamina forming materials that can be
used for this purpose include, for example, poly(vinylpyrrolidone), polyvinylalcohol, polyethylene oxide, a blend of gelatin and polyvinyl-pyrrolidone, gelatin, glucose,
saccharides, povidone, copovidone, poly(vinylpyrrolidone)-poly(vinyi acetate) copolymer

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and mixtures thereof, The water soluble coating can comprise other pharmaceutical excipients that in certain embodiments can alter the way in which the water soluble coating behaves. The artisan of ordinary skill will recognize that the above-noted materials include film-forming polymers. The inert water-soluble coat covering the semipermeable wall and blocking the passageway of osmotic dosage forms ofthe present invention, is made of
synthetic or natural material which, through selective dissolution or erosion can allow the passageway to be unblocked thus allowing the process of osmotic delivery to start. This water-soluble coat can be impermeable to a first external fluid, while being soluble in a
second external fluid. This property can help to achieve a controlled and selective release of
10 the bupropion hydrobromide salt from the osmotic dosage form so as to achieve the desired
in-vitro release rates.

In embodiments where the core ofthe osmotic dosage form does not comprise an osmagent,
the osmotic dosage forms can comprise an osmotic subcoat, which can surround the core of
15 the osmotic dosage form. The osmotic subcoat comprises at least one osmotic agent and at
least one hydrophilic polymer. The osmotic subcoat ofthese embodiments provides for the substantial separation ofthe bupropion hydrobromide salt from the osmotic agent into
substantially separate compartments/layers. This separation can potentially increase the
stability ofthe bupropion hydrobromide salt by reducing possible unfavorable interactions
20 between the bupropion hydrobromide salt and the osmagent, and/or between the bupropion
hydrobromide salt and the components of the controlled release coat. For example, the
osmagent can be hygroscopic in nature, and can attract water that can lead to the degradation

16 ofthe bupropion hydrobromide salt. Since the osmotic agent ofthese embodiments can be
substantially separated from the bupropion hydrobromide salt, the bupropion hydrobromide
25 salt can be less prone to degradation from the water drawn in by the osmagent. The
controlled release coat comprises at least one controlled release polymer and optionally a
plasticizer. The coated cores ofthe osmotic dosage form can be filled into capsules, or
alternatively can be compressed into tablets using suitable excipients. In these embodiments
the osmotic dosage form can utilize both diffusion and osmosis to control drug release, and
30 can be incorporated into sustained release and/or delayed release dosage forms. In addition,
in certain embodiments the osmotic pressure gradient and rate ofrelease ofthe bupropion hydrobromide salt can be controlled by varying the level ofthe osmotic agent and/or the level

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ofthe hydrophilic polymer in the osmotic subcoat, without the need for a seal coat around the osmotic subcoat.

The hydrophilic polymer used in an osmotic subcoat of certain embodiments of the present invention functions as a carrier for the osmotic agent. In certain embodiments the
hydrophilic polymer in the osmotic subcoat does not substantially affect the drug release. In
at least one embodiment, the hydrophilic polymer used in the osmotic subcoat does not act as
a diffusion barrier to the release of the bupropion hydrobromide salt. In at least one
embodiment the release profile ofthe osmotic agent is substantially the same as the release
10 profile ofthe bupropion hydrobromide salt. Such hydrophilic polymers useful in an osmotic
subcoat of certain embodiments ofthe present invention include by way of example,
polyvinyl pyirolidone, hydroxyethyl cellulose, hydroxypropyl cellulose, low molecular
weight hydroxypropyl inethylcetlulose (I-1PMC), polymethacrylate, ethyl cellulose, and
mixtures thereof. In at least one embodiment, thebydrophilic polymer of the osmotic subcoat
15 is a low molecular weight and a low viscosity hydrophilic polymer. A wide variety of low
molecular weight and low viscosity hydrophilic polymers can be used in the osmotic stibcoat. Examples of HPMC polymers that can be used in the osmotic subcoat include
PHARMACOATfi 606, PHARMACOAT fi 606G. PHARMACOAT fi 603, METHOCELfi
E3, METHOCELfi E5, METHOCELfi E6, and mixtures thereof. The hydrophilic polymer
20 ofthe osmotic subcoat can be present in an amount of from about 1% to about 30% by weight

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ofthe osmotic subcoat composition including all values and ranges therebetween. For
example, in certain embodiments the hydrophilic polymer is present in an amount of from
about 1% to about 20%, in other embodiments from about 3% to about 10%, and instill other embodiments about 7% by weight ofthe osmotic subcoat composition.

In at least one embodiment, the osmotic subcoat comprises about 7% PHARMACOATfi
606, about 1% sodium chloride, and about 92% water, by weight ofthe osmotic subcoat composition.

30 One method for producing the osmotic subcoat can be as follows. The at least one osmotic
agent, for example sodium chloride, is dissolved in water. The solution of osmotic agent and water is then heated to about 60°C. The hydrophilic polymer is then added gradually to the solution. A magnetic stirrer can be used to aid in the mixing ofthe hydrophilic polymer to

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the solution of osmotic agent and water. The resultant osmotic subcoating solution can then
be used to coat the core ofthe 5.motic dosage form in a fluidized bed granulator, such as a granulator manufactured by Glatt (Germany) or Aerornatic (Switzerland) to the desired
weight gain. An inlet temperature of from about 10°C to about 70°C including all values and
5 ranges therebetween, in certain embodiments from about 30°C to about 55’C, and in at least
one embodiment from about 40°C to about 45°C; an outlet temperature offrom about 10°C to about 70°C including all values and ranges therebetween, in certain embodiments from about
20°C to about 45°C, and in at least one embodiment from. about 30°C to about 350C; a product temperature of from about 10°C to about 70°C including all values and ranges therebetween,
10 in certain embodiments from about 20°C to about 45°C, and in at least one embodiment from
about 30°C to about 35°C; an air flow of from about 10 cm/h to about 180 exnlh including all values and ranges therebetween; in certain embodiments from about 40 cm/h to about 120
cm/h; and in at least one embodiment from about 60 cm/h to about 80 cm/h; an atomizing
pressure of from about 0.5 bar to about 4.5 bar including all values and ranges therebetween,
15 in certain embodiments from about 1 bar to about 3 bar, and in at least one embodiment at
about 2 bar; a curing temperature of from about 10°C to about 70°C including all values and ranges therebetween, in certain embodiments from about 20°C to about 50°C, and in at least
one embodiment from about 30°C to about 40°C; and a curing time of from about 5 minutes
to about 720 minutes including all values and ranges therebetween; in certain embodiments
20 from about 10 minutes to about 120 minutes, and in at least one embodiment at about 30
minutes. Any other technology resulting in the coating formulation ofthe osmotic subcOat consistent with the objects of the invention can also be used.

The ratio ofthe components in the core, semipermeable membrane and/or water-soluble
25 membrane and/or at least one controlled release coat and/or osmotic subcoat as well as the
amount ofthe various membranes or coats applied can be varied to control delivery ofthe bupropion hydrobromide salt either predominantly by diffusion across the surface ofthe semipermeable membrane to predominantly by osmotic pumping through the at least one passageway in the semipermeable membrane, and combinations thereofsuch that the dosage
30 form can exhibit a modified-release, controlled-release, sustained-release, extended-release,
prolonged-release, bi-phasic release, delayed-release profile or a combination ofrelease
profiles whereby the in-vitro release rates ofthe bupropion hydrobromide salt is such that
after about 2 hours from about 0% to about 20% by weight ofthe bupropion hydrobromide

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salt is released, after about 4 hours from about 15% to about 45% by weight ofthe bupropion hydrobromide salt is released, after about 8 hours, from about 40% to about 90% by weight ofthe bupropion hydrobromide salt is released, and after about 16 hours, more than about
80% by weight ofthe bupropion hydrobromide salt is released. In embodiments where the
5 mode of exit ofthe bupropion hydrobromide salt comprises a plurality ofpores, the amount
ofpore forming agent employed to achieve the desired in-vitro dissolution rates can be
readily determined by those skilled in the drug delivery art.

In at least one embodiment ofthe osmotic dosage form, the core comprises bupropion
10 hydrobromide in an amount of from about 40% to about 99% ofthe core dry weight

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including all values and ranges therebetween. For example in certain embodiments the core comprises bupropion hydrobromide in an amount of about 40%, about 45%, about 50%,
about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about
90%, about 95% or about 99% ofthe core dry weight.

In certain embodiments, the core of the osmotic dosage form comprises at least one means for increasing the hydrostatic pressure inside the membrane or coat. The membrane or coat can
be a semipermeable membrane, a controlled release coat, a water-soluble coat, an osmotic subcoat, or any combination thereof. The core ofthe osmotic dosage form has an effective
20 osmotic pressure greater than that ofthe surrounding fluid in the environment of use so that
there is a net driving force for water to enter the core. The at least one means for increasing
the hydrostatic pressure inside the membrane or coat can be any material that increases the osmotic pressure of the core ofthe osmotic dosage form. The at least one means for
increasing the hydrostatic pressure inside the membrane or coat can be, for example, the
25 bupropion hydrobromide salt, an osmagent, any material which can interact with water and/or
an aqueous biological fluid, swell and retain water within their structure, such as for example
an osmopolymer, and any combination thereof. The osmagent can be soluble or sweliable. Examples of osmotically effective solutes are inorganic and organic salts and sugars. The bupropion hydrobrornide salt can itself be an osmagent or can be combined with one or more
30 other osmagents, such as for example, magnesium sulfate, magnesium chloride, sodium
chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium
sulfate, potassium chloride, calcium carbonate, sodium sulfate, calcium sulfate, potassium
acid phosphate, calcium lactate, d-mamiitol, urea, inositol, magnesium succinate, tartaric

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acid, water soluble acids, alcohols, surfactants, and carbohydrates such as raffinose, sucrose, glucose, lactose, fructose, algin, sodium alginate, potassium alginate, carrageenan, fucoridan, furcellaran, laminaran, hypnea, gum arabic, gum ghatti, gum karaya, locust bean gum, pectin, starch and mixtures thereof. In certain embodiments the core comprises osmagent in an
amount of about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about
45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% ofthe core dry weight.

The osmagent useful in certain embodiments ofthe present invention can be any agent that
10 can generate an osmotic pressure gradient for the transport ofwater from the external
environment ofuse into the osmotic dosage form. Osmagents are also known as osmotically effective compounds, osmotic solutes, and osmotic fluid imbibing agents. Osmagents useful
in certain embodiments ofthe present invention are soluble in aqueous and biological fluids,
such as ionizing compounds, inherently polar compounds, inorganic acids, organic acids,
15 bases and salts. In at least one embodiment the osmagent is a solid and dissolves to form a
solution with fluids imbibed into the osmotic dosage form. A wide variety of osagents can be used to provide the osmotic pressure gradient used to drive the bupropion hydrobromide salt
from the core ofthe osmotic dosage form. Examples of inorganic salts useful as osmagents
include lithium chloride, lithium sulfate, lithium phosphate, magnesium chloride, magnesium
20 sulfate, potassium chloride, potassium sulfate, potassium phosphate, potassium acid
phosphate, sodium chloride, sodium sulfate, sodium phosphate, sodium sulfite, sodium
nitrate, sodium nitrite, and mixtures thereof. Examples ofsalts of organic acids useful as
. osagents include sodium citrate, potassium acid tartrate, potassium bitartrate, sodium
bitartrate, and mixtures thereof. Examples ofionizable solid acids useful as osmagents
25 include tartaric, citric, maleic, malic, fumaric, tartronic, itaconic, adipic, succinic, mesaconic
acid, and mixtures thereof Examples of other compounds useful as osmagents include
potassium carbonate, sodium carbonate, ammonium carbonate, calcium lactate, mannitol,
urea, inositol, magnesium succinate, sorbitol, and carbohydrates such as raffinose, sucrose,
glucose, lactose, lactose monohydrate, a blend offructose glucose and mixtures thereof In at
30 least one embodiment the osmagent is selected from sodium chloride, sodium bromide,
sodium bisulfate, potassium acid tartrate, citric acid, mannitol, sucrose and mixtures thereof. Combinations ofthese osmagents is permissible. The osmagent can be present in an amount offrom about 0.1% to about 50% of the dosage form weight including all values and ranges

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therebetween. For example, in certain embodiments the osmageut is present in an amount of from about 1% to about 40%, and in other embodiments from about 1% to about 20% ofthe dosage form weight.

In certain embodiments, the at least one means for increasing the hydrostatic pressure can comprise, in addition to an osmagent, any material which can interact with water and/or an
aqueous biological fluid, swell and retain water within their structure. In certain
embodiments where the at least one means for increasing the hydrostatic pressure is an
osmopolymer, which can be slightly cross-linked or uncross-linked. The uncross-linked
10 polymers to be used as osmopolyrners, when in contact with water and/or aqueous biological
fluid, preferably do not dissolve in water, hence maintaining their physical integrity. Such

16 polymers can be, for example, chosen from the group of polyacrylic acid derivatives (e.g.,
polyacrylates, poly- methyl methacrylate, poly(acrylic acid) higher alkyl esters, poly(ethylmethacrylate), poly(hexadecyl methacrylate-co-methylmethacrylate),
15 poly(methyiacryiate-co-styrene), poly(n-butyl methacrylate), poly(n-butyl-acrylate),
poly(cyclododecyl acrylate), poly(benzyl acrylate), poly(utylaciylate),
poly(secbutylacrylate), poly(hexyl acrylate), poly(octyl acrylate), poly(decyl acrylate),
poly(dodecyl acrylate), poly(2-methyl butyl acrylate), poly(adamantyl.methacrylate), poly(benzyl methacrylate), poly(butyl methacrylate), poly(2-ethylhexyl methacrylate),
20 poly(octyl methacrylate), acrylic resins), polyacrylamides, poly(hydroxy ethyl methacrylate),
poly(vinyl alcohol), poly(ethylene oxide), poly N-vinyl-2-pyrrolidone, naturally occurring
resins such as polysaccharides (e.g., dextraus, water-soluble gums, starches, chemically modified starches), cellulose derivatives (e.g., cellulose esters, cellulose ethers, chemically modified cellulose, microcrystalline cellulose, sodium carboxymethylcellulose and
25 methylcellulose), starches, CARBOPOLTM, acidic earboxy polymer, CYANAMERTM,
polyacrylamides, cross-linked water-swellable indene-maleic anhydride polymers, GOOD-RITETM, polyacrylic acid, polyethyieneoxide, starch graft copolymers, AQUAKEEPSTM, acrylate polymer, diester cross-linked polyglucan, and any combination thereof.

30 In certain embodiments, the core ofthe osmotic dosage form further comprises a means for
forcibly dispensing the bupropion hydrobromide salt from the core to the exterior ofthe
dosage form. The at least one means for forcibly dispensing the bupropiori hydrobronilde salt can be any material which can swell in water and/or aqueous biological fluid and retain a

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significant fraction ofwater within its structure, and will not dissolve in water and/or aqueous biological fluid, a means for generating a gas, an osmotically effective solute or any combination thereofwhich can optionally be surrounded by a membrane or coat depending on the particular means used. The membrane or coat can be, for example, a membrane or
coat that is essentially impermeable to the passage ofthe bupropion hydrobromide salt, gas
and compounds, and is permeable to the passage of water and/or aqueous biological fluids.
Such a coat or membrane comprises, for example, a semipermeable membrane, microporous membrane, asymmetric membrane, which asymmetric membrane can be permeable, semipermeable, perforated, or unperforated. In at least one embodiment, the at least one
10 means for forcibly dispensing the bupropion hydrobromide salt from the core ofthe osmotic
dosage form comprises a means for generating gas, which means for generating gas is surrounded by, for example, a semipermeable membrane, in operation, when the gas
generating means imbibes water and/or aqueous biological fluids, the means for generating
gas reacts and generates gas, thereby enlarging and expanding the at least one means for
15. forcibly dispensing the bupropion hydrobromide salt unidirectionally or multidirectionally.
The means for generating a gas comprises any compound or compounds, which can produce effervescence, such as for example, at least one solid acid compound and at least one solid
basic compound, which in the presence of a fluid can react to form a gas, such as for
example, carbon dioxide. Examples of acid compounds include, organic acids such as malic,
20 frunaric, tartaric, itaconic, maleic, citric, adipie, succinic and mesaconic, and inorganic acids
such as sulfamic or phosphoric, also acid salts such as monosodium citrate, potassium acid
tartrate and potassium bitartrate. The basic compounds include, for example, metal
. carbonates and bicarbonates salts, such as alkali metal carbonates and bicarbonates. The acid
and base materials can be used in any convenient proportion from about 1 to about 200 parts
25 ofthe at least one acid compound to the at least one basic compound or from about 1 to about
200 parts ofthe at least one basic compound to the at least one acid compound. The means
for generating gas is known.

In at least one embodiment, the at least one means for forcibly dispensing the bupropion
30 hydrobromide salt form the core ofthe osmotic dosage form comprises any material which
can swell in water and/or aqueous biological fluid and retain a significant fraction ofwater
within its structure, and will not dissolve in water and/or aqueous biological fluid, such as for example, a hydrogel. Hydrogels include, for example, lightly cross-linked hydrophilic

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polymers, which swell in the presence of fluid to a high degree without dissolution, usually exhibiting a 5 -fold to a 50-fold volume increase. Non-limiting examples of hydrogels include poly(hydroxyalkyl methaciylates), poly(acrylarnide), poly(methacrlamide), poly(N-vinyl-2-pyrrolidone), anionic and cationic hydrogels, polyelectrolyte complexes, a water-insoluble, water-swellable copolymer produced by forming a dispersion offinely divided copolymers of maleic anhydride with styrene, ethylene, propylene butylenc or isobutylene cross-linked with from about 0.001 to about 0.5 moles of a polyunsaturated cross-linking agent per mole of maleic anhydride in a copolymer, water-swellable polymers or N-vinyl lactams, semi-solid cross-linked poly(vinyl pyrrolidone), diester cross-linked polyglucan hydrogels, anionic
10 hydrogels of heterocyclic N-vinyl monomers, ionogenic hydrophilic gels, and mixtures
thereof. Some ofthe osmopolymers and hydrogels are interchangeable. Such means can optionally be covered by a membrane or coat impermeable to the passage ofthe bupropion hydrobromide salt, and compounds, and is permeable to the passage ofwater and/or aqueous biological fluids. Such a coat or membrane comprises, for example, a semipermeable
15 membrane, microporous membrane, asymmetric membrane, which asymmetric membrane
can be permeable, semipermeable, perforated, or unperforated.

In at least one other embodiment, the at least one means for forcibly dispensing the bupropion hydrobromide salt from the core ofthe osmotic dosage form comprises at least one
20 osmotically effective solute surrounded by a membrane or coat impermeable to the passage
ofthe bupropion hydrobromide salt, and compounds, and is permeable to the passage of
water and/or aqueous biological fluids such that the osmotically effective solute exhibits an osmotic pressure gradient across a membrane or coat. Such coat or membrane comprises, for example, a semipermeable membrane, microporous membrane, asymmetric membrane,
25 which asymmetric membrane can be permeable, semipermeable, perforated, or unperforated.
The osmotically effective solutes include, for example, the osmagents described above.

In embodiments ofthe osmotic dosage form where the means for forcibly dispensing the bupropion hydrobromide salt is surrounded by a membrane or coat, at least one plasticizer
30 can be added to the membrane composition to impart flexibility and stretchability to the
membrane or coat. In embodiments where the means for forcibly dispensing the bupropion hydrobromide salt comprises a means for generating a gas, the membrane or coat preferably is stretchable so as to prevent rupturing ofthe membrane or coat during the period of delivery

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ofthe bupropion hydrobromide salt. Methods of manufacturing such a membrane or coat is known. Plasticizers, which can be used in these embodiments include, for example, cyclic and acyclic plasticizers, phthalates, phosphates, citrates, adipates, tartrates, sebacates, succinates, glycolates, glycerolates, bellzoates, myristates, sulfonamides halogenated phenyls, poly(alkylcnc glycols), poly(alkylenediols), polyesters of alkylene glycols, dialkyl phthalates, dicycloalkyl phthalates, diaryl phthalates and mixed ailcyl-aryl phthalates, such as for
example, dirnethyl phthalate, dipropyl phthalate, di(2-ethylhexyl)phthaiate, di-isopropyl phthalate, diamyl phthalate and dicapryl phthalate; alkyl and aryl phosphates, such as for example, tributyl phosphate, trioctyl phosphate, tricresyl phosphate, trioctyl phosphate,
10 tricresyl phosphate and triphenyl phosphate; alkyl citrate and citrates esters such as tributyl
citrate, triethyl citrate, and acetyl triethyl citrate; alkyl adipates, such as for example, dioctyl adipate, diethyl adipate and di(2-methoxyethyl)adipate; dia&yl tartrates, such as for example, diethyl tartrates and dibutyl tartrate; alkyl sebacates, such as for example, diethyl sebacate, dipropyl sebacate and dinonyl sebacate; alkyl succinates, such as for example, diethyl
15 succinate and dibutyl succinate; alkyl glycolates, alkyl glycerolates, glycol esters and
glycerol esters, such as for example, glycerol diacetate, glycerol triacetate, glycerol
monolactate diacetate, methyl phthalyl ethyl glycolate, butyl phthalyl butyl glycolate,
ethylene glycol diacetate, ethylene glycol dibutyrate, triethylene glycol diacetate, triethylene glycol dibutyrate, triethylene glycol dipropionatc and mixtures thereof. Other plasticizers
20 include camphor, N-ethyl (o- and p-toulene) sulfonamide, chlorinated biphenyl,
benzophenone, N-cyclohexyl-p-toluene sulfonamide, substituted epoxides and mixtures
thereof.

The at least one means for forcibly dispensing the bupropion hydrobromide salt from the core
25 of certain embodiments ofthe osmotic dosage form can be located such that it is
approximately centrally located within the core ofthe osmotic dosage form and is surrounded
by a layer comprising the bupropion hydrobromide salt. Alternatively, the core of the
osmotic dosage form comprises at least two layers in which the first layer comprises the bupropion salt, osmagent and/or osmopolymer and optionally at least one pharmaceutically
30 acceptable excipient adjacent to a second layer comprising the means for forcibly dispensing
the bupropion hydrobromide salt. Alternatively, the core ofthe osmotic dosage form
comprises a multilayered structure in which the layer comprising the bupropion

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hydrobrornide salt is sandwiched between two layers ofthe means for forcibly dispensing the bupropion hydrobromide salt from the osmotic dosage form.

Combinations

The present invention also contemplates combinations ofthe bupropion hydrobromide salt
with at least one other drug. For example, a composition is provided which comprises a first component of bupropion hydrobromide, and a second component of at least one other drug, wherein the two components are each present in an amount effective in the treatment of a condition. The present invention further provides a method for treating a condition,
10 comprising administering to a patient an effective amount of a first component ofbupropion
hydrobromide in combination with an effective amount of at least one other drug. The skilled artisan will know or can determine by known methods which drug combinations are
acceptable. Types of drugs that can be selected as the second drugiiiclude by way of
example other depressants, anti-anxiety agents, steroidal and non-steroidal inflarnmatoris,
15 SSRIs, serotonin receptor agonists, anti-migraine agents, anti-pain agents, anti-emetics, drugs
for treating abuse such as nicotine, appetite modulators, anti-virals, vasodilators, and anti-
pain agents. For example, the other drug can be an antidepressant selected from: monoamine oxidase (MAO) inhibitor, tricyclic antidepressant, serotonin reuptake inhibitor, selective norepinephrine reuptake inhibitors (SNRIs), aminoketones, serotonin antagonists, dopamine
20 reuptake inhibitors, dual reuptake inhibitors, norepinephrine enhancers, serotonin activity
enhancers, dopamine activity enhancers, and combinations thereof. Examples of other drugs
that can be combined with bupropion hyd.robrornide include citalopram, escitalopram, venlafaxine, clozapiie, melperone, amperozide, iloperidone, risperidone, quetiapene,
olanzapine, ziprasidone, aripiprazole, reboxetine, VIAGRAfi, sertraline, paroxetirie,
25 fluoxetine, gabapentin, valproic acid, amitriptyline, lofepraniine, fluvoxarnine, imipramine,
mirtazapine, nefazodone, nortriptyline, SAM-E, buspirone, and combinations thereof. In at
least one embodiment, a combination of bupropion hydrobromide and citalopram is provided.
In at least one other embodiment, a combination of bupropion hydrobromide and
escitalopram is provided: In at least one other embodiment a combination of bupropion
30. hydrobromide and venlafaxine is provided, in at least one other embodiment a combination
ofbupropion hydrobromide and quetiapene is provided.

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In certain embodiments combination products can be made by providing an overcoat that contains at least one other drug. For example, certain embodiments can include a core that comprises bupropion hydrobromide, wherein the core is substantially surrounded by a controlled release coat, which in turn is substantially surrounded by an overcoat that contains
at least one other drug. In certain embodiments the overcoat provides an immediate release ofthe other drug. In addition to the other drug, the overcoat can include at least one low viscosity hydrophilic polymer. The low-viscosity polymer provides for the immediate release ofthe other drug from the overcoat. In at least one embodiment, the low-viscosity polymer
used in the overcoat is hydroxypropyl methylcellulose (HPMC). The overcoat can also
10 include a lubricant such as talc. For example, such embodiments can provide an immediate
release of at least one other drug from the overcoat in a first phase of drug release, and then a subsequent controlled release of the bupropion hydrobromide from the controlled release
coated core in a second phase of drug release.

15 In addition, combinations ofmicroparticles ofthe invention each with a different functional
coating can be combined together in a dosage form. For example, by combining a first group ofuncoated, taste-masked or enteric coated microparticles with a second group of delayed or
sustained release coated microparticles, a pulsatile drug release profile or chronotherapeutic
profile can be achieved. (e.g. see US 5,260,068, US 6,270,805, US 6,926,909,
20 US2002/0098232, US2004/0197405, US 6,635,284, or US 6,228,398).

In other embodiments, the combination can comprise at least 2 different microparticles. For
. example, the combination can include one group ofmicroparticles that provide for a
controlled release of bupropion hydrobromide, and a second group ofmicroparticles that
25 provide for an immediate release ofthe other drug. The microparticles can be combined in a
capsule formulation.

While only specific combinations of the various features and components of the present
invention, have been discussed herein, it will be apparent to those ofskill in the art that
30 desired subsets ofthe disclosed features and components and/or alternative combinations of
these features and components can be utilized as desired.

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As will be seen from the non-limiting examples described below, the coatings of the
invention are quite versatile. For example, the length and time for the lagtime can be
controlled by the rate of hydration and the thickness ofthe controlled release coat. It is possible to regulate the rate ofhydration and permeability ofthe controlled release coat so
5 that the desired controlled release profile can be achieved. There is no general preferred
controlled release coat thickness, as this will depend on the controlled release profile desired. Other parameters in combination with the thickness ofthe controlled release coat include varying the concentrations of one or more ofthe ingredients ofthe controlled release coat composition, varying the curing temperature and length oftime for curing the coated tablet
10 microparticles, and in certain embodiments, varying the level of osmotic agent. The skilled
artisan will know which parameters or combination ofparameters to change for a desired controlled release profile.

STABILITY STUDIES

15 The enhanced stability ofthe bupropion hydrobrornicle salt and compositions containing the
bupropion hydrobrornide salt, in particular when compared to the bupropion hydrochloride
salt and compositions containing the bupropion hydrochloride salt respectively, is evident
from degradation studies performed on the active pharmaceutical ingredient (API), alone, in
the presence of excipients and in the form oftablets (e.g. extended release tablets). The
20 results are described in greater detail in the examples below and in U.S. patent number
7,241,805, the contents ofwhich are incorporated herein by reference.

A comparison ofthe stability ofseveral bupropion salts, including the hydrobrornide, hydrochloride, maleate, tosylate, fumarate, succinate, tartrate and citrate salts, was performed
25 by placing these salts in both open and closed vials in a stability chamber kept at about 40
degrees C and about 75% relative humidity for various periods of time (e.g. 10 days, 13 days,
14 days, 20 days, 24 days, or 32 days). The stability ofthe salts was evaluated based on the formation ofthe main degradation products as determined by HPLC analysis and the %
potency (or assay) ofthe API, after specific time periods in the stability chamber. Time effect
30 ofthe addition of solvents, such as water, ethanol and isopropyl alcohol, was also studied.

The results unexpectedly show that after various periods oftime the hydrobrornide salt of bupropion, on average, showed the least amount of degradation products, particularly when

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compared to the hydrochloride salt. Accordingly the bupropion hydrobromide salt showed greater stability than the hydrochloride salt.

Further stability tests were performed by directly comparing bupropion hydrobromide and
5 bupropion hydrochloride salts in forced degradation studies. These studies were performed
in closed bottles in a stability chamber kept at about 40 degrees C and about 75% relative humidity. At specified times, the material in the bottles was analyzed for the presence of degradation products and % potency (% assay). It was unexpectedly found that the amount ofimpurities was generally lower and the % potency was generally higher for the bupropion
10 hydrobromide salt when compared to the bupropion hydrochloride salt.

Forced degradation studies were also performed on bupropion hydrobromide and bupropion hydrochloride API’s in the presence of standard excipients used in pharmaceutical
formulations. The amount ofthe main degradation products was observed at about 24 and
15 about 48 hours after treatment at about 55°C, at about 55°C and 100% relative humidity, and
at about 105°C. Once again, it was unexpectedly found that the bupropion hydrobromide salt
showed the lowest amount of degradation (as determined by the formation of bupropion
degradation impurities) under these conditions.

20 The stability ofthe tablet formulations of bupropion hydrobromide and bupropion
hydrochloride salts was also compared. With both salts, a single coated tablet having a
controlled release coat (e.g. ETHOCELfi or "BC" coat), as well as a double-coated tablet
. (with a controlled release coat and a moisture barrier coat) were evaluated. The tablets were
placed individually on an open dish, and exposed to the accelerated conditions of about 40°C
25 and about 75% relative humidity in a stability chamber. After 13 days and 20 days, the
samples were assayed and impurity analysis was performed. For the single coated bupropion hydrochloride tablets, the main degradation impurities 3-CBZ and 852U77 were about 0.12%
and about 0.38% respectively, whereas, for the bupropion hydrobromide tablets, these values
were about 0,07% and about 0.49% respectively. The other degradation impurities and the
30 total unknowns were very similar for both products; however, the assay value for the
hydrobromide product was higher than the hydrochloride. The difference in the assay and the impurity levels were more significant in the double coated tablets products. For the same
period ofthe study the assay ofthe bupropion hydrochloride was lower (about 95.5%

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compared to about 98.6% for bupropion hydrobromide) and the level ofthe degradation and total unknowns were higher (3-CBZ: about 0.28%; 852U77: about 1.23%; 827U76: about 0.10%; and total about 1.73%) than the bupropion hydrobromide (3-CBZ: about 0.12%, 852U77: about 0.41%, 827U76: about 0.05%; and total about0.75%).

The stability studies performed herein have demonstrated the unexpected enhanced stability ofbupropion hydrobromide, in particular when compared to bupropion hydrochloride. This enhanced stability is seen with the API form alone, the API form plus excipients, and the extended release and enhanced absorption tablets. The enhanced stability of pharmaceutical
10 formulations comprising bupropion hydrobromide will provide enhanced shelflife and an
ability to withstand storage at higher temperatures and humidity levels when compared with bupropion hydrochloride formulations.

POLYMORPHIC FORMS

15 It is well known that organic molecules can crystallize into solid forms. Moreover the same
organic compound may assume different crystalline arrangements in solid form, depending
on the conditions under which the crystal product is formed. This phenomenon is commonly known as polymorphism. A study was undertaken to explore the polymorphic forms of bupropion hydrobromide. The crystal forms ofthe products obtained in this study were
20 determined by powder X-ray diffraction (PXRD). A RIGAKU miniflex instrument
(Radiation Cu generator 30 KV, filter Ni) was used to obtain the PXRD data. The
results are described, for example in U.S. patent number 7,241,805, the contents ofwhich are incorporated herein by reference

25 BUPROPION-INDUCED SEIZURES

EEG studies, using implanted electrodes to detect electroencephalographic activity in
conscious rats, analyzed the effects of equimolar doses of bupropion hydrochloride and bupropion hydrobromide on central nervous system activity after intraperitoneal
administration. The results (described in greater detail below) show that bupropion
30 hydrobromide has a lower potency for inducing convulsions as well as reducing the severity
of convulsive seizures compared with bupropion hydrochloride. In contrast to bupropion hydrochloride, the bupropion hydrobromide salt form induced fewer convulsions in fewer animals. In still further comparisons, the severity ofseizures observed with bupropion

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hydrobromide were surprisingly observed to be significantly less than the severity of seizures in animals administered bupropion hydrochloride.

The maximum dose ofbupropion hydrobromide administered in the studies on rats
5 was 100 mg/kg, and in the studies on mice was 150 mg/kg. The dose of 150 mg/kg equates
to about 37.5 mg/kg of bromide or about 48.3 mg/kg ofsodium bromide. These therapeutic levels of bromide in which incidences of and/or severity of bupropion-induced seizures are reduced, are surprisingly lower than what one would have expected from the known pharmacological data studying the minimum dosages ofbromide needed for any observable
10 therapeutic benefit. As noted earlier, the level ofbromide required to treat pentylenetetrazole-
induced seizures in mice is known to be 910 mg/kg [M.S. Grewal et al., Journal of Pharmacology And Experimental Therapeutics, Vol. 112, Issue 1, 109-115, 1954].

Certain embodiments ofthe present invention relate to bupropion compositions that
15 comprise safe and pharmaceutically effective amounts of bupropion hydrobromide; wherein
said compositions unexpectedly provide for fewer incidences ofseizures and/or less severe seizures associated with the administration of bupropion hydrobromide than an otherwise
similar or identical composition containing an equivalent molar amount ofbupropion hydrochloride.
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Additional Embodiments

Further embodiments ofthe invention described herein and enabled by the present description include the following:
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Certain embodiments include bupropion hydrobromide and 3’-chloro--2-bromo-
propiophenone. 3 ’-chloro-2-bromo-propiophenone is an impurity associated with the
preparation of bupropion hydrobromide. In certain embodiments, 3’-chloro-2-bromo-propiophenone is present in an amount that is non-genotoxic; or in an amount that would
30 result in a daily exposure ofnot more than ("NMT") about 1.5 big/day in the drug product.
Certain embodiments contain less than about 1.5 1ug of 3’-chloro-2-bromo-propiophenone.
For example in certain embodiments the 3chloro2bromopropiophdnonc impurity is
present in an amount of less than about 1.5ig, 1.4jig, 1.3 jig, 1.2ig, 1.1g, 1.0.tg, 0.9tg,

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0.8.tg, 0.7ug, 0.6g, 0.5j.g, 0.4tg, 0.3.tg, 0.2.tg, O.1ig, 0.09tg, 0.08ug, 0.07ug, 0.06p.g, 0.05g, 0.044g, 0.03.tg, 0.02tg, or 0.01tg, including all values and subranges therebetween.
In at least one embodiment the 3’-chloro-2-bromo-propiophenone impurity is present in undetectable amounts, wherein the limit of detection is 1.0Lg, or ippm.

In certain embodiments the 3-chlorobenzoic acid degradation product is limited in the drug product to about 0.7% or less. In at least one embodiment the 3-chlorobenzoic acid
degradation product is limited in the composition to about 0.5% or less. In at least one
further embodiment the 3-chlorobenzoic acid degradation product is limited in the
10 composition to about 0.3% or less.

In certain embodiments the moisture content in the drug product is limited to not more than about 2.0%. In certain embodiments the moisture content is limited to not more than about
2.0% after a storage time of about 1 minute when stored in a closed container using a Karl
15 Fischer apparatus and UPS Method 1. For example in certain embodiments the moisture

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content after a storage time of about 1 minute when stored in.a closed container using a Karl Fischer apparatus, and USP Method 1, is less than about 2.0%, 1.9%, 1.8%, 1.7%, 1.6%,
1.5% 1.4%, 1.3%, 1,2%, 1.1%, 1.0%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1%, including all values and subranges therebetween,

In another embodiment there is a tablet comprising (i) a core and (ii) a controlled release
coat, said core comprising:
(a) bupropion I-iBr;
(b) binder (e.g. polyvinyl alcohol); and
25 (c) lubricant (e.g. glyceiyl behenate - Compritolfi 888);
said controlled release coat (e.g., "SMARTCOAT") comprising:
(d) water-insoluble water-permeable film-forming polymer (e.g, ethyl cellulose grade PR
100);
(e) plasticizer (e.g, polyethylene glycol 4000, dibutyl sebacate, or a mixture thereof);
30 (f) water-soluble polymer (e.g. polyvinylpyrrolidone - Povidonefi USP);
wherein in the controlled release coat the ratio of(d):(e):(f) = from about 3:1:4 to about 5:1:2; orfl’om about 7:2:6 to about 19:5:18; or about 13:4:12; or about 13:6:16;;
the tablet optionally further comprising a moisture barrier coat;

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said optional moisture barrier coat comprising:

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(g) enteric polymer (e.g, an acrylic polymersuch as methacrylic acid copolymer type C - Eudragitfi L30 D-55);
h) permeation enhancer (e.g. silicon dioxide - Syloidfi 244FP); and
(i) plasticizer (optional) - (e.g. mixture oftriethyl citrate and polyethylene glycol 4000 - Carbowaxfi 4000).

In another embodiment there is a once-daily modified release pharmaceutical composition comprising 522 mg of bupropion hydrobromide, said composition providing an in-vivo
10 plasma profile selected from:

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Mean Tmax of from about 2 hours to about 7 hours;
Mean Cmax olfrom about 113 ng/ml to about 239 ng/ml;
Mean Cmin of from about 18 ng/ml to about 44 ng/mi; and
Mean AIJCO-t offrom about 1236 ng-hr/ml to about 2224 rig-hr/mi.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising 348 mg of bupropion hydrobromide, said composition providing an in-vivo plasma profile selected from:
Mean Tmax offrom about 2 hours to about 7 hours;
20 Mean Cmax of from about 96 ng/ml to about 172 ng/ml;
Mean Cmin offrom about 17 ng/ml to about 36 ng/ml; and
Mean ATJCO-t offrom about 1063 ng-hr/ml to about 1755 ng-hr/ml.

In another embodiment there is a once-daily modified release pharmaceutical composition
25 comprising bupropion hydrobromide, said composition providing a mean Tmax of from
about 2 hours to about 7 hours.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean Tmax that is
30 substantially equivalent to that of a once-daily modified release pharmaceutical composition
comprising bupropion hydrochloride.

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In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean Tmax that is from about 80% to about 125% ofthat of a once-daily modified release pharmaceutical
composition comprising bupropion hydrochloride.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean Cmax that is substantially equivalent to that of a once-daily modified release pharmaceutical composition comprising bupropion hydrochloride.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean Crnax that is from about 80% to about 125% ofthat of a once-daily modified release pharmaceutical composition comprising bupropion hydrochloride.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean Cmin that is substantially equivalent to that of a once-daily modified release pharmaceutical composition comprising bupropion hydrochloride.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean Crnin that is from about 80% to about 125% ofthat of a once-daily modified release pharmaceutical composition comprising bupropion hydrochloride.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean AUCO-t that is substantially equivalent to that of a once-daily modified release pharmaceutical composition comprising bupropion hydrochloride.

In another embodiment there is a once-daily modified release pharmaceutical composition comprising bupropion hydrobromide, said composition providing a mean AIJCO-t that is

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from about 80% to about 125% ofthat of a once-daily modified release pharmaceutical composition comprising bupropion hydrochloride.

In another embodiment there is a modified release pharmaceutical composition comprising:
a core comprising a therapeutically effective amount of bupropion, hydrobromide; and
a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat surrounds at least a part ofsaid core; and
wherein the amount of bupropion hydrobromide released at a time point from about 0 hours
10 to about 16 hours, in the presence of at least 5% ethanol, using USP Apparatus I at 75 rpm
and 37 – 0.5 °C, is less than the amount of bupropion hydrobromide released at the same time point in 0.1 N HCl using USP Apparatus I at 75 rpm and 37 – 0.5 °C.

In another embodiment there is a modified release pharmaceutical composition comprising:
15 a core comprising a therapeutically effective amount of bupropion hydrobromide; and
a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat surrounds at least a part of said core; and
wherein the amount of bupropion hydrobromide released at a time point from about 0 hours
20 to about 16 hours, in the presence of at least 5% ethanol, using USP Apparatus I at 75 rpm
and 37 – 0.5 °C, is less than about 125% ofthe amount of bupropion hydrobromide released
at the same time point in 0.1 N HC1 using USP Apparatus I at 75 rpm and 3.7 – 0.5 °C.

In another embodiment there is a modified release pharmaceutical composition comprising:
25 a core comprising a therapeutically effective amount of bupropion hydrobromide; and

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a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat at least partially surrounds said core; and
wherein dose dumping does not occur in the presence of 0.1 N HCl with 40% EtOH.

In another embodiment there is a method ofreducing dose dumping comprising
administering to a subject a modified release pharmaceutical composition comprising:
a core comprising a therapeutically effective amount of bupropion hydrobromide; and

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a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat at least partially surrounds said core.

In another embodiment there is a pharmaceutical composition comprising 522 mg of
bupropion hydrobromide, said composition providing an in-vivo plasma profile selected
from:
Mean Tmax of from about 2 hours to about 7 hours;
Mean Cmax of from about 115 ng/ml to about 235 ng!ml;
10 Mean Cmin of from about 20 ng/ml to about 40 ng/ml; and
Mean AUCO-24hr of from about 1240 ng-hr/ml to about 2220 ng-hximl.

In another embodiment there is a pharmaceutical composition comprising 522 mg of bupropion hydrobromide, said composition providing an in-vivo plasma profile selected
15 from:
Mean Tmax of about 4 hours;
Mean Cmax ofless than about 200 nWml; and
Mean AUCO-24hr ofmore than about 2000 ng-hr/mI.

20 In another embodiment there is a once-daily modified release pharmaceutical composition
comprising bupropion hydrobromide, said composition providing a mean Tmax that is substantially equivalent to that ofthe same once-daily modified release pharmaceutical composition comprising bupropion hydrochloride instead ofbupropion hydrobromide.

25 In another embodiment there is a once-daily modified release pharmaceutical composition
comprising bupropion hydrobromide, said composition providing a mean Tmax that is from about 80% to about 125% ofthat ofthe same once-daily modified release pharmaceutical composition comprising bupropion hydrochloride instead of bupropion hydrobromide.

30 In another embodiment there is a modified release tablet comprising
(i) a core comprising
(a) a therapeutically effective amount ofbupropion hydrobroniidc;
(b) a binder; and

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(c) a lubricant; and

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(ii) a control-releasing polymeric coat at least partially surrounding said core;
wherein said modified release tablet provides for the controlled release ofsaid bupropion hydrobromide from said modified release tablet over a period of about 24 hours; and
wherein said modified release tablet has improved stability when compared to an otherwise similar or identical modified release tablet comprising an equivalent molar amount of
bupropion hydrochloride instead of bupropion hydrobromide, when each are stored for at
least about 12 months at about 25°C and at about 60% relative humidity.

10 In another embodiment there is a modified release bupropion hydrobromide tablet suitable for
oral administration comprising
(i) a core comprising
(a) a therapeutically effective amount of bupropion h.ydrohromidc;
(b) a binder; and
15 (c) a lubricant;
(ii) a controlled release polymeric coat which at least partially surrounds said core; and
(iii) a degradation product chosen from 3-chlorobenzoic acid, 827U76, 20U78, 852U77, and mixtures thereof;
wherein said modified release bupropion hydrobromide tablet contains less of said
20 degradation product as compared to an otherwise similar or identical modified release tablet
containing an equivalent molar amount of bupropion hydrochloride instead of bupropion hydrobromide;
when the modified release bupropion hydrobromide tablet and the otherwise similar or
identical modified release tablet-containing bupropion hydrochloride are each are stored for at
25 least about 12 months at 25°C and 60% relative humidity after tablet formulation.

In another embodiment there is a modified release tablet comprising:
a therapeutically effective amount of bupropion hydrobromide;
wherein at about 12 months after formulation ofsaid modified release tablet, at about 37–
30 0.5°C, from about 0% to 40% ofsaid bupropion hydrobromide is released after 2 hours; from
about 40% to about 75% ofsaid bupropion hydrobromide is released after 4 hours; not less
than about 75% ofsaid bupropion hydrobromide is released after 8 hours; and not less than

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about 85% ofsaid bupropion hydrobromide is released after 16 hours, in 900m1 of 0,1 N MCi using USP Type 1 apparatus with a rotational speed of 75 rpm.

In another embodiment there is a modified release pharmaceutical composition comprising:
5 (i) a core comprising a therapeutically effective amount of bupropion hydrobromide; and

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(ii) a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat at least partially surrounds said core; and
wherein said cQrnposition is resistant to alcohol-induced dose dumping.

In another embodiment there is a modified release pharmaceutical composition comprising:
(i a core comprising a therapeutically effective amount of bupropion hydrobromide; and
(ii) a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
15 wherein said coat at least partially surrounds said core; and
wherein the rate of release of bupropion hydrobromide in dissolution, media containing
alcohol is slower than the rate ofrelease ofbupropion hydrobromide in dissolution media not containing alcohol,

20 In another embodiment there is a modified release pharmaceutical composition comprising:
(1) a core comprising a therapeutically effective amount of bupropion hydrobromide; and
(ii) a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat at least partially surrounds said core; and
25 wherein the amount of bupropion hydrobromide released at a time point from about 0 hours
to about 16 hours, in dissolution media comprising about 40% EtOH and 60% 0.1N HCl,

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using USP Apparatus Type 1 at 75 rpm, is not more than the amount of bupropion hydrobromide released at the same time point in dissolution media comprising about 100% 0.1N HCl using USP Apparatus Type II at 75 rpm.

In another embodiment there is a modified release pharmaceutical composition comprising:
(i) a core comprising a therapeutically effective amount of bupropion hydrobromide; and

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(ii) a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
wherein said coat at least partially surrounds said core; and
wherein the amount of bupropion hydrobromide released at a time point from about 0
minutes to about 120 minutes, in dissolution media comprising about 40% EtOH and 60%
0.1N HC1, using USP ApparatuType 1 at 75 rpm, is not more than the amount of bupropion hydrobromide released at the same time point in dissolution media comprising about 100%
0.1N HC1 using USP Apparatus Type 1 at 75 rpm.

10 In another embodiment there is a method ofresisting alcohol-induced dose dumping of
bupropion hydrobromide comprising administering to a subject a modified release pharmaceutical composition, said composition comprising:
(i) a core comprising a therapeutically effective amount ofbupropion hydrobromide; and
(ii) a controlled release polymeric coat comprising a water-insoluble polymer and a water-
15 soluble polymer;
wherein said coat at least partially surrounds said core.

In another embodiment there is a method of treating a subject at risk of alcohol-induced dose dumping ofbupropion hydrobromide and in need of bupropion treatment, the method
20 comprising administering to a subject a modified release pharmaceutical composition, said
composition comprising:
(i) a core comprising a therapeutically effective amount of bupropion. hydrobromide; and
(ii) a controlled release polymeric coat comprising a water-insoluble polymer and a water-soluble polymer;
25 wherein said coat at least partially surrounds said core.

In another embodiment there is a composition comprising bupropion hydrobromide and 3’- chloro-2-bromo-propiophenone.

30 In another embodiment there is a composition comprising bupropion hydrobromide and less
than about 1.5 ig of 3’-chloro-2-bromo-propiophenone.

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In another embodiment there is a composition comprising bupropion hydrobrorinde and less than about 1.0 ig of 3 -chloro-2-bromopropiophenone.

In another embodiment there is a modified release composition comprising bupropion hydrobromide wherein the moisture content is not more than about 2.0% in said composition after a storage time of about 1 minute, when, stored in a closed container using a Karl Fischer apparatus, USP Method 1.

In another embodiment there is a composition comprising bupropion hydrobromide and at
10 least one pharmaceutically acceptable exeipient, wherein the amount of bupropion
hydrobromide is chosen from 174mg, 348mg and 522mg.

In another embodiment there is a modified release tablet comprising bupropion hydrobromide and at least one pharmaceutically acceptable excipicnt, wherein the amount ofbupropion
15 hydrobromide is chosen from 174mg, 348mg and 522mg.

In another embodiment there is a modified. release tablet comprising bupropion hydrobromide and at least one pharmaceutically acceptable excipient, wherein the amount ofbupropion hydrobromide is chosen from 174mg, 348mg and 522mg; and wherein the bupropion
20 hydrobromide is contained within a core of the tablet further comprising a controlled release
coating over the core.

In another embodiment there is a composition comprising at least bupropion hydrobromide in
the concentration specified in one ofA, B, and C in the following Table admixed with one or
25 more additional components listed in A, B and C in the following Table:

B

Component
3upropion Hydrobromide 174 mg 348 mg 522 mg
Polyvinyl Alcohol 5.8 mg 11,6 mg 22.5 mg
Glyceryi Behenate
Target Core Tablet.Weight
(mg)

5.8 mg
185.6 mg

11.6 mg
371.2 mg

22.5 mg,
567 mg

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thyIce11u1ose 100, NP 15.4 mg 16.4mg 18.13 rug
ovidone (K-90) 9.5 rug 10.2 rug 21.87 mg
Polyethylene Glycol, 4000. 3.4 mg 3,7 mg 5.33 mg
)ibutyl Sebacate (DBS) 1.7 mg 1.8 mg 2.67 mg
Target Coating Weight Gain
(mg)

30 mg b 32 mg H 48 mg

Carnauba Wax Trace Amount [race Amount
Denatured Ethyl Alcohol, 200
roof

Evaporated Off Evaporated Off Evaporated Off

Ethyl Alcohol, 190 proof Evaporated Off Evaporated Off Evaporated Off
Purified Water Evaporated Off Evaporated Off Evaporated Off
Opacode R Black Ink Trace Amount Trace Amount Trace Amount
Isopropyl AiŁohol,99% None None None
Final Printed Tablet Weight
(mg)

216 rug 403 mg 615 mg

In another embodiment there is a composition comprising at least about 522 mg of bupropion hydrobromide and at least one pharmaceutically acceptable excipient. In other aspects ofthis embodiment the composition is in tablet form. In other aspects ofthis embodiment the composition is a modified release formulation. In other aspects ofthis embodiment the composition is in tablet form and the bupropion hydrobromide is contained within a core of
the tablet further comprising a coating over the core. In other aspects ofthis embodiment the coating is a controlled release coating.

10 In another embodiment there is a composition comprising bupropion hydrobromide and at least one pharmaceutically acceptable excipient;
wherein administration of an amount ofthe bupropion hydrobromide to a first rat results in
less incidences of and/or less severe bupropion-induced seizures when compared to
incidences of and/or severity of bupropion-induced seizures resulting from administration of
15 an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity of bupropion-induced seizures are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode.

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In another embodiment there is a modified release tablet comprising bupropion hydrobromide and at least one pharmaceutically acceptable excipient;
wherein administration of an amount ofthe bupropion hydrobromide to a first rat results in
5 less incidences of and/or severity ofbupropion-induced seizures when compared to
incidences of and/or severity of bupropion-induced seizures resulting from administration of
an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity ofbupropion-induced seizures are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode.
10

In another embodiment there is a composition comprising bupropion hydrobromide and at

40 least one pharmaceutically acceptable excipient;
wherein administration of about 100mg/kg ofthe bupropion hydrobromide to a first rat
results in less incidences of and/or severity ofbupropion-induced seizures when compared to
15 incidences of and/or severity of bupropion-induced seizures resulting from administration of
an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity of bupropion-induced seizures are measured by electroencephalogram analysis using a hippocampally implanted depth electrode.

20 In another embodiment there is a method of treating a subject at risk of bupropion-induced
seizures in need of bupropion treatment, the method comprising:
administering a composition comprising bupropion hydrobromide to said subject in an
amount sufficient to treat said subject.

25 In another embodiment there is a method oftreating a subject at risk of bupropion-induced
seizures in need ofbupropion treatment, the method comprising:

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administering a composition comprising bupropion hydrobromide to said subject in an
amount sufficient to treat said subject; wherein the composition comprises an amount of bupropion hydrobromide chosen from 174mg, 348mg and 522 mg.

In another embodiment there is a method oftreating a subject at risk of bupropion-induced seizures in need of btipropion treatment, the method comprising:

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administering a composition comprising bupropion hydrobromide to said subject in an
amount sufficient to treat said subject; wherein the composition comprises an amount of bupropion hydrobromide chosen from 1 74. g, 348mg and 522 mg; wherein the composition
is in a modified release tablet form; wherein the tablet comprises a controlled release coating;
5 and wherein the administering comprises oral administration.

In another embodiment there is a method ofreducing incidences ofbupropion-induced
seizures comprising: administering a pharmaceutically effective amount of bupropion hydrobromide to a subject in need ofbupropion administration;
10 wherein the incidences of and/or severity of bupropion-induced seizures resulting from the
administration of bupropion hydrobromide is less than incidences of and/or severity of bupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride.

15 in another embodiment there is a method ofreducing incidences of and/or severity of
bupropion-induced seizures comprising:
administering a pharmaceutically effective amount of bupropion hydrobromide to a subject in need of bupropion administration;
wherein administration of about 100mg/kg ofthe bupropion hydrobromide to a first rat
20 results in less incidences of and/or severity ofbupropion-induced seizures when compared to
incidences of and/or severity of bupropion-induced seizures resulting from administration of
an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity of bupropion-induced seizures in the first and
second rats are measured by an electroencephalogram analysis using a hippocampaily
25 implanted depth electrode.

In other embodiments of assessing the incidences of and/or severity of bupropion induced seizures,.a phenotypic assessment of the subject is assessed. For example, a mild seizure can
be characterized by a little jerking ofthe head, a, moderate seizure can be characterized by
30 some jerking ofthe head, and severe seizures can be characterized by strong jerking ofthe
head.

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In another embodiment there is a method ofreducing the incidences and/or the severity of bupropion induced seizures by coadmiuistration of a bromide salt with a bupropion salt, wherein the bromide salt is administered in an amount ofless than about 3.5 mg/kg. In other aspects ofthis embodiment, the bromide salt is administered in amounts offrom about 1.0 to
5 about 3.5 mg/kg, inclusive of 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6
mg/kg, 1.7 mg/kg, 1.75 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3
mg/kg, 2.4 mg/kg, 2.5 mg/kg, 2.6 mg/kg, 2.67 mg/kg, 2.7 mg/kg, 2.8 mg/kg, 2.9 mg/kg, 3.0
mg/kg, 3.1 mg/kg, 3.2 mg/kg, 3.3 mg/kg, 3.4 mg/kg, and all values and ranges therebetween.
In other aspects ofthis embodiment, the bromide salt is a sodium bromide salt. In other
10 aspects ofthis embodiment, the bupropion salt is a hydrochloride salt.

10 In at least one embodiment there is a composition comprising bupropion hydrobromide and at
least one pharmaceutically acceptable excipient; wherein administration of an amount (e.g.
about 1 00mg/kg) of a bupropion hydrobromide to a first rat results in less incidences of
15 and/or severity ofbupropion-induced seizures when compared to incidences of and/or
severity of bupropion-induced seizures resulting from administration of an equivalent molar
amount of bupropion hydrochloride to a second rat; wherein the bupropion hydrobromide that
is administered to the first rat is from a source other than the composition (i.e. the bupropion hydrobromide that is administered to the first rat is not extracted from the composition);
20 wherein the bupropion hydrobromide that is administered to the first rat can be the same form
as the bupropion hydrobromide that is in the composition; and wherein the incidences of
and/or severity of bupropion-induced seizures are measured by an electroencephalogram
analysis using a hippocampally implanted depth electrode.

25 The examples below are non-limiting and are representative of variousaspects of certain
embodiments ofthe present invention.

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EXAMPLES

EXAMPLE 1: PREPARATION OF BUI’ROPION HBR SALT

Bupropion HBr salt was prepared according to the method shown in Scheme 1:

Scheme 1

Bromination Reaction

3 ’-chloro-propiophenone
MW= 168.62

ci)::ç)LyBr

0

Br2 ci1))L-
CH2C17 L Br

2-bromo-3Lch1oropropiophcnonc
MW = 247.52

Amination Reaction

t-butylamine

CH2Cl2 c1OA(
C(CH3)3

2-t-butylamino-3 ’-chioro-propiophenone MW= 239.75

Work Up / Precipitation / Drying

C1 11?

HN

C(CH3)3

1) work up toluene
2) precipitation:
IPA, HBr gas
3) drying

Finishing Step

Bupropion.HBr Sieving Bupropion,HBr Intermediate Packaging Final Release

(a) Brornination and condensation reactions

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0

Cl

Bf
C(CH3)3

Bupropion.HBr
Intermediate

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3-Chloro-propiophenone starting material was brominated in methylene chloride by dropping bromine under controlled conditions. On reaction completion the mother liquor was worked up and then the second reaction was executed by transferring the bromoderivative solution onto the tert-butylantine. The second substitution reaction (the tertbutylantiue amino -group
5 substitutes the bromine atom) forms the final bupropion molecule. After work up of the
mother liquor, a bupropion toluene solution was obtained. The solvent was evaporated and bupropion was dissolved in isopropanol. From the isopropanol solution, the hydrobromide
was precipitated with hydrogen bromide gas. On precipitation completion, the product was centrifuged, washed with isopropanol and dried under vacuum. On dryer discharge approval
10 it was discharged in Kraft drums within double polyethylene bags.
ill the last finishing step, the above intermediate was sieved to obtain the Release which was packed in Kraft drums within double polyethylene bags.

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Elemental analysis ofthe bupropion HBr was carried out using a Fi.sons Elemental Analyser
BA 1108. The results were consistent with the molecular formula of bupropion HBr.

EXAMPLE 2: BUPROP1ON HBr EXTENDED RELEASE (XL) TABLETS
The aim of this example was to describe the development of bupropion HBr XL 1174 and 348mg). Granulation, tabletting and coating procedures are all described thoroughly in this example. In-vitro testing was conducted on the cores, the ethylcellulose coated cores and the
20 final coated tablets in order to determine which formulation gave the desired results.
From their structural formulae, it is observable that the difference between bupropion HC1
and bupropion HBr is the salt. This, of course, results in a different molecular weight.
However, these differences were taken into account in the present study, and modifications
were made in order to obtain in-vitro correlation results to the bupropion HCl using
25 dissolution studies.

It was previously observed that when 15 0mg of bupropion HCl was tested for its release of bupropion, the base value that was released was 130mg. However, when 150mg of
bupropion HBr was tested., the base value released was only 112mg. Thus, the amount of bupropion HBr had to be increased in order to increase the base value from 112mg to 130mg,
30 which was the target. Studies showed that 174mg ofbupropion HBr gave a base value
release of 130mg and is therefore why 174mg was used as opposed to 150mg bupropion HBr. Bupropion HBr XL - Granulation Process

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A summary ofthe manufacturing process used for the preparation of bupropion HBr XL
tablets is shown in Figure 1.
The following materials were used in the granulation ofthe immediate release core ofthe bupropion HBr BA tablets: bupropion HBr, polyvinyl alcohol (PVA) and purified water.
5 Once granulated, lubricant (COMPRITOLfi 888) was added to complete the formulation.
Each Trial was divided, into 5 parts. The percentage ofAPI in each formulation was 93.75%;
the percentage ofPVA in each formulation was 3.125%. A summary ofthe breakdown of
each trial per part is described in Table 1.
The PVA was dissolved into the purified water using a magnetic stirrer and a clear colourless
10 solution was made.
The NIRO Fluid Bed was used to granulate the bupropion HBr Granules with the PVA
solution in a process known as wet massing. Figure 2 shows a summary ofthe granulation procedure.
The Bupropion HBr was loaded into the fluid bed and granulation was initiated. The
15 specifications that were used as guidelines are listed in Table 2,
Loss on Drying was determined after each granulation using the Moisture Analyzer, A 1 g
sample was taken and loaded into the moisture analyzer. The sample ran for 5 minutes at a temperature of 105°C.
Upon completion of each batch part’s granulation, the five parts were combined together.
20 They were hand screened using Mesh No. 14 (1.4mm) and any oversized granulation was
passed through the Com.il fitted with a 2mm screen.
COMPRITOLfi 888 was used as a lubricant in the formulation. The screened bupropion HBr
granules and the COMPRITOLfi 888 were loaded into the V-blender and were blended for 5

1 minutes. The COMPRITOLfi 888 made up 3.125% ofthe formulation. The final granule
25 batch size is described in Table 3.
Bupropion HBr XL - Tabletting Process
The Beta Press was used to compress the Bupropion]’Br tablets. Depending on the dose of
the tablet, 174mg or 348mg, different tooling sets were used. The 7mm punches were used to
compress the 174mg tablets and 9mm and 10mm. punches were used to compress the 348mg
30 tablets, Tooling was polished prior to each run.
The tablet weights were determined as being 185.6mg for the 174mg dose tablets and
371.2mg for the 348mg dose tablets. These adjustments to tablet weight were made order
to compensate for the fact that bupropion HBr was being used in place of bupropion HC1.

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The individual tablet weights had a control limit of –5%, and the average tablet weight had a control limit of–3% (using ten tablets).
A hardness tester was used to determine the load required to diametrically break the tablets crushing strength) into two equal halves. A predetermined range set the specifications for
5 hardness, which was 6.0-12.0 SC for both the 174mg and 348mg tablets.
Friability was determined using tablets that equaled a weight of 6.5g in a friabilir 4 minutes at 25 rpm. Tablets were dc-dusted before and after testing. A weight loss ofless
than 0.8% was used as the criteria in order to accept or reject a batch.
Table 4 summarizes the specifications ofthe tablet press set-up. All the specifications were
10 kept within the range and at the setting that was assigned, throughout all ofthe batches.
Table 5 summarizes the specifications that were kept constant throughout the compression of
all the batches.

The flow chart shown in Figure 2 describes the steps that led up to and including the
tablettiug process. Figure 3 shows a summary ofthe tabietting procedure.
15 Bupropion HBr XL - Coating Process
A summary of the coating process used for the coating of the Bupropion HBr XL tablets is
shown in Figure 4. The first coat is an ethylcellulose (e.g. ETHOCELfi) coat that controls
 the release, which is followedby a final coat that acts as a moisture barrier.
For the ethylcellulose coating and final coating of the Bupropion HBr XL tablets, the 15
20 inches O’Hara Labcoat II System was used. An attached spraying nozzle and a propeller

mixer were also used.

Several ethylcellulose coating solutions were developed and used to coat the Bupropion HBr tablets. The ethylcellulose coating layer was placed on the tablets containing one ofthe formulations listed in Table 6.

25 In fonnulation 1, ethyl Alcohol 95% and IPA 99% were combined together in a stainless steel
container. While stirring, PEG 4000 was added and allowed to dissolve. Once dissolved, ethylcellulose (e.g. ETHOCELfi) was added and left to stir for 30 minutes. Then, Povidone
was added to the solution and was mixed for an overnight period (15-20 hours).
In formulation 2, PE04000 was placed into a beaker with the Dibutyl Sebacate and was
30 stirred until it dissolved. Ethyl Alcohol 95% was added accordingly in order to allow the
PEG 4000 to completely dissolve. In a separate stainless steel container, the remaining Ethyl Alcohol 95% was placed and, while being stirred, ethylcellulose was added and stirred for 30

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minutes. Following that, Povidone was added and allowed to stir for an overnight period
(15-20 hours).
In formulation, Ethyl Alcohol 95% was placed in a stainless steel container. While stirring, PEG 4000 was added and allowed to dissolve. Once dissolved, ethylceliulose was added and
5 left to stir for 30 minutes. Then, Povidone was added to the solution and was mixed for an
overnight period (1520 hours).
Two Final coating solutions were developed and used to coat the Bupropion HBr tablets after they had been first coated with the ethylceliulose coat.
One ofthe following formulations shown in Table 7 was used to coat the tablets with a final
10 coat.

In Formulation A, the purified water was placed in a glass beaker and Chroma-Tone DEB
5 156-CLE was added and allowed to mix for 15 minutes. The EUDRAGITfi was passed through a Mesh screen (no. 60) prior to use. Following this, the EUDRAGITfi was added to the beaker and was stirred for 15 more minutes.
15 In Fonulation B, part 1 ofthe Purified Water was placed into a glass beaker and PEG 4000
was added to it and allowed to mix until it was completely dissolved (5 minutes). The
Triethyl Citrate was then added and left to mix for another 5 minutes. Once dissolved, the
solution was then added to the EUDRAGITfi Suspension and left to stir for 45 minutes. The EUDRAGITfi was passed through a Mesh screen (no. 60) prior to use. In a separate beaker,
20 part 2 ofthe purified water was added to the SYLOIDfi 244FP and mixed until it was
completely dissolved (10 minutes). Finally the SYLOIDfi Suspension was added to the
EUDRAGITfi Suspension and left to stir for another 10 minutes.
ITable 8 summarizes the specifications that were monitored in the ethylcellulose coating process and their ranges.
25 Table 9 summarizes the specifications that were monitored in the final coating process and
their ranges.
In-vitro Studies on the Bupropion HBr cores
Dissolution was performed on the Bupropion HBr cores, on the different weight gains of
ethyicellulose coated cores and on the different weight gains of final coated tablets. USP-1
30 method was used to conduct these studies. The dissolution test was performed using 900rnL
of 0,1N HC1 and at a speed of 75im. Samples were taken at every hour for 16 hours. The dissolution profiles were obtained by plotting the cumulative percent ofAPI dissolved against sampling time points. Sink conditions were maintained throughout all the experiments.

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On several trials, USP-3 method was used to conduct the dissolution studies. These dissolution tests were performed for 16 hours total with the following breakdown: 2 hours using 900mL of Simulated Gastric Fluid (SOP) at pH 1.2 with 0.5% of Sodium Lauryl
Sulfate (SLS), followed by 2 hours in 900mL of Acetate Buffer at a pH of 4.5, followed by
5 12 hours in 900mL of Phosphate Buffer Simulated Intestinal Fluid (SIF) at a pH of U.
These results were plotted with the in-vivo data and the Bupropion HCI data in order for a comparison to be made.
Study on Batch BUP-HBr-XL-009-5
The formulation was granulated using NIRO Fluid Bed. After granulation was completed,
10 the batch was screened and then prior to compression the lubricant (COMPRITOLfi 888)
was added. The final blend was compressed into 348mg tablets using the Beta press with
9mm and 10mm standard, round, concave tooling. Table 10 describes the amounts of each material in the granulation of the 348mg tablets. A first compression run was done to
produce tablets with different hardness values so as to determine the effects of hardness, if
15 any, on the dissolution (Figure 5). Dissolution was conducted on the 348mg cores in order to
determine their release (Figure 6).
The granulation results show that the average granulation time is 2.0 hours and the average
LOD % is 0.345%. Tables 11 and 12 summarize the theoretical and actual values ofthe

parameters that were monitored in the compression process using the 9mm and 10mm
20 tooling, respectively.
In order to determine the tablet hardness for this study, tablets of different hardness values
were compressed and dissolution was conducted on them to see the difference.
Tablets with a hardness of 41p, 6-71cp and 9-1 Okp were compressed and the dissolution
profiles of each were shown in Figure 5. It was observed that there was no significant
25 difference between the three different hardness ranges.
The dissolution profiles ofthe 348mg (Figure 6) and 174mg cores (Figure 7) showed that the cores were releasing approximately 100 percent ofAPI in an hour.
Dissolution ofthe 10mm, 348mg cores was done also in order to see ifthese tablets released faster when compared to the 9mm cores due to their larger surface area (Figure 7).
30 When the dissolution results ofthe 9mm and 10mm cores were compared (Figure 8), the
10mm cores showed no difference from the 9mm cores. Thus, the 10mm cores were no
longer manufactured or used in this study.
Study on Batch BIJP-HBr-XL-021-5

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The Formulation was granulated-using NRO Fluid Bed. The final blend was compressed
into 174mg tablets using the Beta press with 7mm standard, round, concave, stainless steel tooling. Table 13 describes the amounts of each material in the granulation of the 174mg tablets. It was noted that the 348 and the 174mg tablets had the same composition and
5 amounts of each material; the only variation was the tablet weight, which, was adjusted at the
compression stage. Dissolution was conducted on the 174mg cores in order to see their
release (Figure 9).
The granulation results show that the granulation time is 2 hours 6 minutes and the average LOD % is 0.26%. Table 14 summarizes the theoretical and actual values ofthe parameters
10 that were monitored in the compression process using the 7mm tooling.
The dissolution profile ofthe 174mg (Figure 9) showed that the cores were releasing approximately 100 percent ofAPI in an hour.
Study on Batch BUP-HBr-XL-3 48mg-0 13-5
Using 348mg tablets, an ethylceliulose (e.g. ETHOCELfi or "EC") coating followed by a
15 Final coating, were sprayed onto the tablets using the O’Hara Labcoat II Coating Equipment.
The materials used in the ethylcellulose coating, their percent contribution to the total
solution, the amounts of each in the batch and the percentage ofthe solids in the solution
were all listed in Table 15.

The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C;
20 Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 2 hours and 25 minutes to coat the tablets with a weight gain of 32mg, Tablet weights
were taken and recorded in Table 16 at 28mg, 30mg, 32mg, and 34mg weight gains.
. The dissolution profile (Figure 10) shows that the tablets with the 34mg weight gain of
ethylcellulose coating released Bupropion HBr the slowestwhcn compared to the others and
25 that the tablets with the 28mg weight gain released Bupropion HBr the fastest when
compared to the other weight gains.
The materials used in the final coating, their percent contribution to the total solution, the
amounts of each in the batch, the amount ofsolid contribution in grams and the percentage of
the solids in the solution were all listed in Table 17.
30 The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40°C;
Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
After this trial run, Chroma-Tone was no longer used due to the formulation problems it
caused. First, it limited the composition ofthe formulation due to its inflexibility, as

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SYLOIDfi, PEG and Triethyl Citrate ratios could not be varied. Second, the solution foamed and coagulated, which in turn caused the process for making the coating solution to be
changed from the original so that it did not re-coagulate. Chrorna-Tone can, however, still be considered an option for the formulation but different grades and mixtures would need to be
5 used and made in order to accommodate the Bupropion HBr XL tablets.
It took 31 minutes to add a 7mg weight gain ofthe final coating solution to the tablets.
Tablet weights were taken and recorded in Table 18 at 4mg, 5mg, 6mg and 7mg weight
gains.
The dissolution profile (Figure 11) shows that the tablets with the 7mg weight gain of Final
10 coating released the slowest when compared to the other two weight gains (5mg and 6mg
weight gains).
Study on Batch BtJP-HBr-XL-348mg-018-5
Using 348mg tablets, an ethylcellulose coating followed by a final coating, were sprayed onto the tablets using the 0 ’Hara Labcoat II Coating Equipment.
15 The materials used in the ethylceliulose (e.g. ETHOCELfi) coating, their percent
contribution to the total solution, the amounts of each in the batch and the percentage of the solids in the solution were all listed in Table 19.

The parameters are as follows: Spray Rate: 13 g./rnin; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
20 The coating process ofthis trial took 2 hours and 13 mindtes to obtain a 32mg weight gain.
Tablet weights were taken and recorded in Table 20 at 26mg, 28mg, 30mg, and 32mg weight

gams.

Figure 12 shows that the tablets with the 30mg and 32 mg weight gain of ethylcellulose
coating solution released at almost the same rate. The tablets with the 321ng weight gain
25 released slower than the tablets with the 30mg weight gain in the first 5 hours of dissolution.
After 6 hours, the tablets with the 32mg weight gain released slightly faster than those with a 30mg weight gain. The f2 similarity factor confirmed that the release rate ofboth weight
gains was similar (91.32%).
The materials used in the final coating, their percent contribution to the total solution, the
30 amounts of each in the batch, the amount ofsolid contribution in grams and the percentage of
the solids in the solution were all listed in Table 21.

The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40°C; Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.

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It took 41 minutes to add a 7mg weight gain ofthe final coating solution to the tablets.
Tablet weights were taken and recorded in Table 22 at 4mg, 5mg, 6mg, and 7mg weight
gains.
Figure 13 shows the release profile of the tablets with the 7mg weight gain of Final coating.
5 Study on Batch BUP-HBrXL-174mg-022-5
Using 174mg tablets, an ethylcellulose coating followed by a final coating, were sprayed onto the tablets using the O’Hara Labcoat Ii Coating Equipment,
The materials used in the ethylcellulose (e.g. ETHOCELfi) coating, their percent
contribution to the total solution, the amounts of each in the batch and the percentage ofthe
10 solids in the solution were all listed in Table 23.
The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 4 hours and 30 minutes to add a 30mg weight gain ofthe ethylcellulose coating
solution to the tablets. Tablet weights were taken at 20mg, 22mg, 24mg, 26mg, 28mg, 29mg,
15 and 30mg weight gains and were recorded in Table 24.
Figure 14 shows the % dissolved of each ofthe samples with different weight gains of ethylcellulose coating (22mg, 24mg, 28mg and 30 mg weight gains). From the graph, it was
evident that the tablets with the 30mg weight gain of ethylcellulose coating released slower
than the other weight gains. When the release rates ofthe tablets with the 30mg and the
20 28mg weight gains were compared, there was only a slight difference noticed in the release.
The f2 similarity factor confirmed the similarity ofthe two releases (92.34%).
The materials used in the final coating, their percent contribution to the total solution, the
. amounts of each in the batch, the amount ofsolid contribution in grams and the percentage of
the solids in the solution were all listed in Table 25.
25 The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40°C;
Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 1 hour and 26 minutes to add a 7mg weight gain ofthe final coating solution to the
tablets. Tablet weights were taken and recorded in Table 26 at 4mg, 5mg, 6mg, and 7mg
weight gains.
30 The dissolution profile (Figure 15) shows that the tablets with the 7mg weight gain offinal
coating released the slowest, in comparison to the 5mg and the 6 mg weight gains.
Study on Batch BUP-.HBr-XL-348mg-.023 5

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Using 348mg tablets, an ethylcellulose coating was sprayed onto the tablets using the O’Hara Labcoat II Coating Equipment.
The materials used in the ethylcellulose (e.g. ETHOCELfi) coating, their percent contribution to the total solution, the amounts of each in the batch and the percentage ofthe solids in the solution were all listed in Table 27.
The parameters are as follows: Spray Rate: 13 gimin; Pan Speed: 12.0 rpm; Inlet Air: 50’C,-

Product 0°C;Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 2 hours and 16 minutes to add a 32mg weight gain ofthe ethylcellulose coating
solution to the tablets. Tablet weights were taken at 26mg, 28mg, 30mg, and 32mg weight
10 gains and were recorded in Table 28.
The dissolution profile (Figure 16) shows that the tablets with the 32mg weight gain of Sethylcellulose coating, when compared to the tablets with the 26mg, 28mg and the 30mg weight gain of ethylcellulose coating, released at the slowest rate.
Study on Batch BTJP-HBr-XL-348mg-0255
15 Using 348mg tablets, an ethylcellulose coating followed by a final coating, were sprayed onto
the tablets using the O’Hara Labcoat II Coating Equipment.
The materials used in the ethylcellulose (e.g. ETHOCELfi or EC) coating, their percent
contribution to the total solution, the amounts of each in the batch and the percentage ofthe
solids in the solution were all listed in Table 29.
20 The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C;
Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 2 hours and 13 minutes to add a 32mg weight gain ofthe ethylcellulose coating

5 solution to the tablets. Tablet weights were taken at 26mg, 28mg, 30mg, and 32mg weight
gains and were recorded in Table 30.
25 The dissolution profile (Figure 17) shows that the tablets with the 32mg weight gain of
ethylcellulose coating when compared to those with 26mg weight gain released slower in the
beginning and then faster after 7 hours. When comparing the tablets with 32mg weight gain
of ethylcellulose coating to those with 30mg weight gain of ethylcellulose coating, the tablets
with the 32mg weight gain released slower up until 10 hours. The £2 similarity factor showed
30 that the release of the tablets with the 30mg and 32mg weight gains were in fact similar
(93.72%).

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The materials used in the final coating, their percent contribution to the total solution, the amounts of each in the batch, the amount ofsolid contribution in grams and the percentage of the solids in the solution were all listed in Table 31.
The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40°C; Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
The coating solution was altered for this batch by changing the percentage ofsolid from each ofthe solid components in the solution. The percentage of EUDRAGITfi solid contribution
was decreased from 65% to 56.5%. The percentage of SYLOIDfi, CARBOWAXfi and Triethyl Citrate were increased from 25%, 6,65% and 3.39% to 30%, 9% and 4.5%,
10 respectively.
It took 40 minutes to add a 7mg weight gain ofthe final coating solution to the tablets.
Tablet weights were taken and recorded (Table 32) at 4mg, 5mg, 6mg, and 7mg weight gains. The dissolution profile (Figure 18) shows that the tablets with the 7mg weight gains released
the slowest of the three samples tested. However, f2 calculation showed that the tablets with
15 the 6mg weight gain released similarly to those with the 7mg weight gain of Final coating
(93.33%).
Study on Batch BUP-HBr-XL-348mg026-5
Using 348mg tablets, an ethylceilulose coating was sprayed onto the tablets using the O’Hara
Labcoat II Coating Equipment.
20 The materials used in the ethylcellulose (e.g. ETHOCELfi or EC) coating, their percent
contribution to the total solution, the amounts of each in the batch and the percentage ofthe
solids in the solution were all listed in Table 33.

40 The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C;
Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW,
25 It took 2 hours and 11 minutes to add a 32mg weight gain ofthe ethylcellulose coating
solution to the tablets. Tablet weights were taken at 26mg, 28mg, 3 0mg, and 32mg weight
gains and were recorded in Table 34.
The dissolution profile (Figure 19) shows that the tablets with the 32mg weight gain of
ethylcellulose coating released the slowest when compared to the other three samples with
30 lower weight gains of ethylcellulose coating (26mg, 28mg and 3 0mg).
Study on Batch BIJP-HBr-XL-174mg-027--5
Using 174mg tablets, an ethylcellulose coating followed by a final coating, were sprayed onto
the tablets using the O’Hara Labcoat II Coating Equipment.

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The materials used in the ethylcellulose (e.g. ETHOCELfi or EC) coating, their percent contribution to the total solution, the amounts of each in the batch and the percentage of the solids in the solution were all listed in Table 35.
The parameters are as follows: Spray Rate: 13 g/miu; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 3 hours and 29 minutes to add a 32mg weight gain ofthe ethylceilulose coating
solution to the tablets. Tablet weights were taken at 22mg, 24mg, and 26mg weight gains
and were recorded in Table 36.

The dissolution profile (Figure 20) shows that the tablets with the 26mg weight gain of
10 ethylcellulose coating released the slowest ofthe three samples tested.
The materials used in the final coating, their percent contribution to the total solution, the Samountsin each in the batch, the amount ofsolid contribution in grams and the percentage of the solids in the solution were all listed in Table 37.
The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40°C;
15 Product Temperature: 35°C – 5°C; and Supply Air Flow: 200 CFW.
It took 1 hour and 17 minutes to add a 7mg weight gain ofthe final coating solution to the
tablets. Tablet weights were taken and recorded in Table 38 at 4mg, 5mg, 6mg, and 7mg
weight gains.
The dissolution. profile (Figure 21) shows that the tablets with the 7mg weight gain of final
20 coating initially released slower that the tablets with 4mg, 5mg and 6mg weight gains.
However, at approximately 12 hours, all 4 samples were releasing similarly.

09 EXAMPLE 3: ASSESSMENT OF BTJPROPION HYDROCHLORIDE AND BIJPROP1ON
HYDROROMIDE AT CONVULSIVE AND NON-CONVULSIVE DOSES ON
25 CORTICAL EEG IN MICE

Initially a behavioral study was conducted to evaluate proconvulsant activities in CD-i mice
comparing bupropion hydrochloride and bupropion hydrobromide. The studies showed that
the seizure activity in mice was more severe with bupropion hydrochloride than with
bupropion hydrobromide. These studies, however, were limited to observable behavioral
30 differences between the two salt forms ofbupropion, and did not measure nonobservable
differences (e.g. electroencephalographic activity). Therefore, EEG was employed to study
the seizure inducing effects ofthese drugs and quantify the EEG effects of bupropion hydrochloride and bupropion hydrobromide at a range of doses.

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The study evaluated the cortical mouse electroencephalogram (BEG) effects ofbupropion hydrochloride and bupropion hydrobromide at five doses over the range of 100-15 0mg/kg. A comparison ofthe effects of equimolar doses of bupropion hydrochloride and bupropion hydrobromide salts by EEG monitoring in the mouse was conducted.
5 Test system: 30 healthy female mice, ofstrain CD- 1, having a bodyweight of 25-29 g, were acclimatized for a minimum period of 4 days and used for this study. Each animal, after allocation to groups, was identified by markings on the dorsal surface ofthe tail.
Environmental conditions included a temperature of 22–3°C, and artificial lighting of 12
hours light/dark cycle. Routine activities such as cleaning, feeding and watering were
10 performed according to the RCS1’s current SOPS.

15

The diluent used was 0.9% sodium chloride solution. Storage temperature was at about 25°C. The appropriate amount of bupropion salt(bupropion hydrochloride or bupropion
hydrobromide) was added to 0.9% sodium chloride solution to give the desired concentration.
Test Item Dose Level Quantity of Salt Volume of Dose Volume
(mg/kg body wt) (g) Saline (mL) (mL/kg)
Bupropion 100 0.05 5 10
Hydrochloride
Bupropion 125 0.0625 5 10
Hydrochloride
Bupropion 150 0.075 5 10
Hydrochloride

Test Item Dose Level Quantity of Salt Volume of Dose Volume
(equivalent to (g) Saline (mL) (mL/kg)
mgofthe HlCl
salt/kg body-..wt)
Bupropion 100 0.058 5 10
Hydrobromide
Bupropion 125 0.0725 5 10
Hydrobromide
Bupropion 150 0.087 5 10
Hydrobromide

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Test Item Administration: The test item was administered intraperitoneally using a disposable syringe with a 1 ml syringe and 26g needle. The route of administration was intraperitoneal. Animals were dosed once with the exception ofthose that received 100mg/kg of each salt, which were re-tested with a higher dose (115mg/kg) the following week. Bupropion hydrochloride and bupropion hydrobromide were initially tested at 150mg/kg in side-by-side comparison. Subsequently they were tested at 125mg/kg, 1 00mg/kg and then n=2 each) at 135mg/kg and 115mg/kg.
Protocol: Habituated mice were anesthetized with isofolurane, placed in a stereotaxic frame
and maintained normothermic (36-37°C) by means of a feedback-controlled mouse-designed
10 homeothemiic blanket (Harvard Apparatus). Under isoflurane anaesthesia, a midline skill
incision was made over the skull and the skull exposed. Three partial craniectomies were performed: one overlying each temporal lobe and a third across the region overlying frontal cortex. Mouse-sized cranial EEG (E363/20, electrode with mounting screw and socket,
Plastics One Inc) were affixed at each point. The electrode assembly was affixed to the skull
15 with dental cement and then anaesthesia discontinued and the animal placed in the recording
chamber for 30-60 minutes after recovery. Electrodes were then connected to a multichannel
363 Connector Cable system with SL6C 6 channel swivel commutator and baseline EEG recordings commenced using a Grass model Comet Portable 40-channel Digital EEG &
Review System with Twin digital EEG in tandem with continuous digital video, After a
20 baseline video-EEG recording for 10 minutes, mice were injected with bupropion
hydrochloride or bupropion hydrobromide (100, 115, 125, 135 or 150mg/kg, i.p,). Mice were run in parallel so that a hydrochloride mouse was injected within minutes of a hydrobromide mouse and recordings made simultaneously. Video-EEG was recorded for a period of one (1) hour. Afterwards, mice were returned to cages and then euthanized at 24h and brains
25 harvested.

Analysis: The duration oftype IV polyspike high frequency (1Hz) high amplitude (2 X baseline) was determined for each mouse over the 1 h recording period,
Results: Generally, 150mg/kg triggered strong seizure-like behavior within 5 minutes of
injection with either salt. This was most pronounced during the early recording time (first 15-
30 20 minutes) but episodic events continued through the hour ofrecording. However, for study
pairs 1, 2 and 3 the convulsive behavior ofthe hydrobromide-treated mouse lasted longer
than the hydrochloride-treated mouse (in some cases up to 30 min more). For, example the second hydrochloride-treated mouse ceased any seizure-like behavioural activity in about 30

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mins after injection while we were still observing rearing and falling, forepaw running and turning in the hydrobromide-treated mouse at 60 minutes.
EEG At 150mg/kg (n = 4 per salt) essentially no seizure EEG was detected. Very brief (2-3 s) bursts were detected within the first 5 minutes after injection that coincided with the onset
5 ofseizure-like behavior. No other EEG seizures were detected in any mice with either salt
after that time despite ongoing"behavioural" seizures (e.g. convulsions).
Set 1 HCl: EEG - no seizure EEG; HBr - single, very briefseizure
Set 2 HC1: EEG -two very brief’EEG bursts; HBr, no seizure EEG
Set 3 HCl: EEG - brief burst ofseizure; HBr, brief burst ofseizure BEG
10 At 125 mg/kg (n = 4 per salt) some significant seizure EEG was recorded. In this case there
was a tendency for more seizure bursts in the bupropion hydrochloride animals. The quantitation ofthis is shown below.
Total Duration (seconds)
Bupropion Hydrochloride

Total Duration (seconds)
Bupropion Hydrobromide
290 30
130 25
115 0
0 0
MEAN 133.8 MEAN 13.8
SD 119.3 SD 16.0
P value t-test 0.093

Number of Events
Bupropion Hydrochloride

Number ofEvents
Bupropion Hydrobromide
12 2
8 1
10 0
0 0
MEAN 7.5 MEAN 0.75
SD 5.259911 SD 0.957427
15 P value t-test 0.045

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No type IV seizure bursts of any significance were captured in any mouse with either
salt at 100 mg/kg (n2); 135 mg/kg (n=2); or 115 mg/kg (n2).
There appears to be a small difference between the two salts in the number ofseizure
EEG bursts elicited at one dose: 125 mg/kg. The magnitude ofthis difference was
compromised by the fourth pairing test because neither animal expressed seizure EEC.
Cortical EEG recordings picked up very brief events at the 150 mg/kg dose but these
occurred equally between the salts. No significant seizure EEC events were detected at the
other doses tested. The explanation for why no seizure EEG was detected at the higher 150.
mg/kg dose which caused profound convulsive behavior is not known. It may reside with
10 subcortical pathway activation and inhibition. Depth electrode recordings might yield
explanations for this lack of EEC result at the 150 mg/kg dose. An additional point is that
S even at the 125 mg/kg dose there appears to be a variable effect ofthe salts on EEC. The
reason for this is not clear but we suggest the following: (i) Simple and inherent in-vivo
biological variability; (ii) A CD 1 mouse-specific genotype effect; (iii) The use offemale
15 mice (introducing, perhaps, oestrous cycle events); (iv) Higher than previous mouse study
weight. All the CD mice we used were 25g and above, which may be higher than was
previously used for behavioural testing.
There may be a small difference in seizure EEC between the two salts of bupropion at one
dose (125 mg/kg). However, the data reveal the convulsions triggered by this drug in mice do
20 not commonly manifest as epileptiform seizure EEC as detected by cortically-mounted

electrodes.

EXAMPLE 4: EVALUATION OF BUPROPION HYDROCHLORIDE AND BUPROPION HYDROBROM1DE FOR EFFECTS ON THE EEC TRACE IN THE RAT

25 A further comparison ofthe effects of equimolar doses of bupropion hydrochloride and bupropion hydrobromide salts by EEC trace monitoring in the rat was conducted.
The effects ofthe two bupropion salt forms hydrochloride and hydrobromide on
central nervous system activity after intraperitoneal administration were evaluated by means ofEEC trace monitoring in conscious rats. The method which detects
30 electroencephalographic activity in conscious rats follows that described by Dürmüller et al.,
(2000) Vigilance-Controlled Quantified EEC in Safety Pharmacology, Current Protocols in Pharmacology Unit 10.6. The study was conducted at Porsolt & Partners Pharmacology, Research Laboratory, Z.A. des Suhards - B.P. 9, 53940 Le Genest-Saint-Isle, France.

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Materials and General Methods:
Substances: The formulation excipient used was physiological saline (Laboratoire
Aguettant). The bupropion hydrochloride salt and bupropion hydrobromide used were from Biovail Technologies Ireland Ltd., and provided as white powders and dissolved in
5 physiological saline. All substances were stored in a dry, dark, controlled access area and
maintained at a controlled ambient temperature of about 20 –3°C. The vehicle solutions were stored at about +4°C. The substances were administered in a volume of 5 mllkg body weight. The doses of bupropion hydrochloride are expressed in mg/kg of salt. The doses of
bupropion hydrobrornide are expressed in mg/kg ofthe bupropion hydrochloride molar
10 equivalent (correction factor = 1.16). The substances were dissolved in physiological saline
and prepared freshly at each day of experimentation.
Test systems: The rats used were male Rj: Wistar (Han) rats, weighing from about
280 g to 324 g at the time ofimplantation. They were supplied by Elcvage Janvier, 53940 Le Genest-Saint-Isle, France. The characteristics ofthe animals used (age, species and strain)
15 are comparable with those described in the scientific literature. Upon delivery to the
laboratory, the animals were housed in groups of 5 animals maximum, in maerol,on cages (44
x 28 x 19 cm) containing wood litter (Litalabo - SPPS, 95100 Argenteuil, France). The
animals had free access to food (Code 113 - SAFE, 89290 Augy, France) and tap water. The
animal house was maintained under artificial lighting (12 hrs) from 7:00 to 19:00 in a
20 controlled ambient temperature of about 21 – 3°C and relative humidity maintained at from
about 30% to about 80%. After implantation, the animals were kept individually in macrolon
cages (30 x 18 x 19 cm) in a separate room for implanted animals under the same
environmental conditions as before. Except during the test sessions, the animals had free Saccessto food (Code 113) and tap water. The animal were identified by marking the
25 connector fixed on the animal’s head with an indelible pen. Rats were sacrificed at the end of
the experiments by lethal injection of pentobarbital (100 mg/kg i.p.). Animals were not
submitted to necropsy. There is no reason to expect that contaminants were present in the
feed, water or bedding at levels capable of interfering with the results ofthe tests. No checks
were performed for this particular study,
30 For the EEG signal acquisition, the software 10X2 and for the visual off-line analysis, the
software ECG auto (both from EMKA Technologies, France) were used.
Experimental Procedure:

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Electrode implantation procedure: Implantation surgery was carried out under aseptic
conditions. Rats, anesthetized with sodium pentobarbital (60 mg/kg i.p., plus supplementary doses offrom about 5mg/kg to about 10 mg/kg to maintain anesthesia until surgery
completion) were implanted with 2 surface EEG electrodes, comprised ofminiature titanium
5 screws, placed bilaterally over the frontal-parietal cortex and 2 depth electrodes, comprised of
twisted platinium-iridium wires, placed stereotaxically into the hippocampus CA3 area
(Paxinos and Watson coordinates interaural: AP +5.0 mm, L –2,5 mm, V +7.0 mm). An additional screw, placed over the right occipital cortex, served as ground electrode. The
electrodes were connected to small plugs and the whole assembly was secured on the skull
10 with dental acrylate. Following surgery, implanted animals were kept in individual macrolon
cages (30 x 18 x 19 cm and were allowed at least 10 days to recover. A total of 27 rats were implanted.
Apparatus: For the EEG recording, the animals were placed in rectangular Plexiglas
cubicles (30 x 10 x 25 cm) mounted on treadmills. Five recording units were run in parallel.
15 A turning commutator was attached above the centre of each cubicle, about 30 cm above
walking level. On one side, it was connected via an electrically shielded multicore cable to
the animal and on the other side to the signal conditioning system (Coulbourn Model V75-
01). The system filters were set for all channels to high pass 1 Hz and low pass 150 Hz, respectively. The amplification levels were kept at from I 000x to l0000x. The EEG signals
20 were acquired and processed on a PC (DELL GX620-2800) installed with a 16 channel
200kHz/12-bit AD acquisition card NI PCI-6023E). This PC was integrated in a local
network (Ethernet), which also included a PC for the data analysis, and a CD writer for data storage.
Testing procedure: Before beginning ofthe testing procedure, the rats were
25 habituated in a 1 hour training session connecting to the recording cable and treadmill
walking. A few minutes before launching the first recording, the animals were transferred
from the holding to the testing room, connected to the recording cable, and placed into the recording cubicle. The EEC signals were briefly inspected for their quality and amplification levels adjusted as necessary. The animals were then given a 1 hour recording session without
30 any treatment (baseline control) with intervals of 10 minutes with the treadmill alternatively
turned on (walking speed: 1.8 nn/mm) and off. Immediately after the end ofthe baseline
control recording, animals were administered (i.p.) bupropion hydrochloride or bupropion hydrobromide and recorded for another 2-hour session. 23 hours after the injection, the

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animals were given a 1 hour recording session under the same experimental conditions as the day before. Then the same recording procedure as on the previous day was followed. The
same animal was always run on the same treadmill, and was connected to the same unit ofthe signal conditioning system. The treadmills were always operated with the same recording
5 cables.

Data acquisition and analysis: The EEG signal was digitized at a sampling rate of 500 Hz/recording-channel and the data stored in raw data files. The analysis was performed off-
line by visual inspection ofthe traces. The cortical and hippocampal traces were displayed individually for each rat on the computer screen at a time resolution of 10 sec/window. The
10 windows then were scrolled and halted when a signal showed irregularity and the sequence
was noted. Representative samples ofpathologic signals were saved in pdf-format files for presentation in the report. Spike trains or spike-and-wave activity clearly exceeding baseline amplitudes and lasting at least one second were defined as seizure activity.
EEG Observations:

15 As shown in Tables 39(1)-(4) and 40(i)-(4): Isolated and infrequent atypicil EEG events ofprobably non-pathologic character were observed on various occasions at all doses. Some events were observed before and after substance administration and do not appear
directly to be linked to or predispose to seizure activity. In 3 rats, however, short seizure
activity was observed in the hippocampus, in all cases before bupropion hydrochloride
20 administration which may indicate that those rats were epilepsy prone. On the other hand, all
3 rats were administered substance the day before (10, 30 and 60 mg/kg respectively).
At 10 mg/kg, no seizure activity was observed in either cortex or hippocampus in any rat administered bupropion hydrochloride or bupropion hydrobromide.
At 30 mg/kg, apart from one rat with a short seizure activity in the hippocampus, during the
25 pre-administration phase (Fig. 22, rat Q0343, HCI group), no seizure activity was observed in
either cortex or hippocampus in any rat administered bupropion hydrochloride or bupropion hydrobrornide.
At 60 mg/kg, apart from one rat with a short seizure activity in the hippocampus
during the pre-administration phase (Fig. 23, rat Q0337, HCl group), no seizure activity was
30 observed in either cortex or hippocampus in any rat administered bupropion hydrochloride or
bupropion hydrobromide.
At 100 rug/kg, one rat was observed with a short seizure activity in the hippocampus
during the pre-administration phase. In addition, all 10 rats administered bupropion

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hydrochloride had from 1 to 4 Seizures, and 4/9 rats administered bupropion hydrobromide had 1 seizure (Fig. 24 A and B rat Q0348, bupropion hydrochloride group; Fig. 25 A and B rat Q0352, bupropion hydrobromide group).
Seizures generally started in the cortex and were shorter in the hippocampus than in
the cortex with both salt forms. Seizure onset delay was very short for both salt forms, approximately 3 minutes on the average for the hydrochloride salt and approximately 2
minutes for the hydrobromide salt. Seizure duration was from 15 to 50 seconds in the cortex. Comparing to the first seizure phase, there was no clear difference in the mean seizure
duration between the two salt forms in both the cortex and the hippocampus (Tables 41 and
10 42(1)-(2)). Taking the multiple occurrences of seizures into account, the overall seizure
duration ofthe bupropion hydrochloride group was longer than that ofthe bupropion hydrobromide group.
BEG Trace monitoring in the rat: Figures 22 and 23 show traces of 10 seconds of
hippocampal activity. The amplitude scales are expressed in volts [V]. In figure 22,
15 hippocampal seizure activity of about 3 seconds duration in rat Q0343 is shown and in figure
23, a similar activity in rat Q0337. Figures 24 A and B show traces of 10 seconds of cortical (FIG. 24A) and hippocampal (FIG. 24B) activity. The amplitude scales are expressed in volts [VJ. The initial phase of seizure activity in both the cortex and hippocampus in rat Q0348 is shown. The rat was administered bupropion hydrochloride at 100 mg/kg. Figures 25 A and
20 25B show traces of 10 seconds of cortical (FIG. 25 A) and hippocampal (FIG. 25 B) activity.
The amplitude scales are expressed in volts [V]. The initial phase ofseizure activity in both
the cortex and hippocampus in rat Q0352 is shown. The rat was administered bupropion hydrobromide at 100 mg/kg.
Behavioural Observations:

25 As shown in Tables 39(l)-(4) and 40(1)-(4): At 10 mg/kg, no abnormal behavior was observed apart from one rat in the bupropion hydrobromide group which had a short lasting facial clonus while being connected to the recording system. Since it happened before
launching the data acquisition, that event was not captured by the BEG.
At 30 mg/kg, all rats administered the bupropion hydrochloride salt, but none the
30 bupropion hydrobromide salt, showed stereotypies/hyperactivity.
At 60 mg/kg, all rats administered either the bupropion hydrochloride or bupropion hydrobromide salt showed stereotypies/hyperactivity. One rat in the bupropion hydrobromide group had a fatal whole body clonus immediately after administration before being connected

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to the recording system. Since it happened before launching the data acquisition, that event was not captured by the EEC.
At 100 mg/kg, all rats administered either the bupropion hydrochloride or bupropion hydrobromide salt showed stereotypies/hyperactivity. The convulsions expressed by either
form ofbupropion appeared as facial clonus with or without additional rearing and forelimb clonus. The difference in the number ofrats having seizures was statistically significant (p
0.05) (Table 41).
The results ofthis study show that bupropion hydrobromide has a lower potency for
inducing convulsions compared with bupropion hydrochloride. in contrast to bupropion
10 hydrochloride, the bupropion hydrobromide salt form induced fewer convulsions in fewer
animals. The behavioral convulsions were mild, and were accompanied by electrical seizures activity. The short seizure activities observed in the hippocampi of 3 rats are most likely incidental findings, since they occurred in an apparent random fashion. There were, however unexpected immediate reactions observed in one rat administered 10 mg/kg and one rat
15 administered 60 mg/kg bupropion hydrobromide which may ask for further testing.

EXAMPLE 5: CONVULSANT ACTIVITY OF HYDROCHLORIDE AND
HYDROBROMIDE SALTS OF BUPROPION
I.

20 Two studies were performed to investigate the relative proconvulsant properties ofthe two bupropion salts. In the first instance a range finding study was performed to establish the appropriatr dose range for the main study. In each study the mice were divided into two dose groups and
injected intraperitoneally with either bupropion HCl or bupropion HBr.
Post-treatment, mice were continuously observed for a period of 120 minutes followed by
25 periodic observation at 135 minutes, 150 minutes, 165 minutes, 180 minutes, 210 minutes, 240
minutes, 300 minutes and 24 hours for incidence and intensity of clonic convulsions. A clonic convulsion was defined as a stiffening ofthe animal followed by jerking movements. The
convulsions were classified as mild, moderate and severe according to the following descriptions.

30 Mild: Head and tail slightly extended and little jerking
Moderate: Head and tail fully extended with some jerking
Severe: Head and tail fully extended with strong jerking

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Range finding study

The CD-1 mice were divided into dose groups (N= 3/dose group) and injected intraperitoneally with the following doses ofBupropion HO 75, 100, 125 or 150 mg/kg with a parallel series of dose groups administered with an equimolar dose range ofBupropion HBr. Post-treatment findings recorded included continuous observation for 120 minutes for evidence of clonic convulsions, and
intennittent (fixed) observations for 24 hours for other signs, including tonic convulsions,
movement, activity, paralysis, gait and evidence ofrecovery.

Main study
10 The CD-i mice were divided into dose groups (N= 10/dose group) and injected intraperitoneally
with the following doses of Bupropion HCl 100, 125 or 150 mg/kg with a parallel series of dose

46 groups administered with an equimolar dose range ofBupropion HBr. Post-treatment, mice were

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continuously observed for a period of 120 minutes for incidence and intensity of clonic convulsions.
Results

15 Range finding study

20

The Bupropion HBr had an apparently higher threshold (125 mg/kg) for tonic convulsions
than Bupropion HC1 group (100 mg/kg) and a tendency to recover more quickly from other treatment-related signs. It was found that the incidence and intensity of clonic convulsions provided
a quantal basis for comparison ofthe two treatments and are summarized in the Table below.

Incidence and intensity of clonic convulsions in CD-1 mice dosed intraperitoneally with Bupropion HC1 or Bupropion HBr (Range-finding study, N=3/dose group).

Mean Number of Convulsions/Mouse

Dose (mg/kg) Bupropion HCl Bupropion HBr
75 0 0
100 1.0(2/3) 0
125 6.0(3/3) 8.0(3/3)
150 32.0(3/3) 11.0 (3/3)
Dose level is quoted as t3upropion 1-IUI. Bupropion HBr is dosed at equimolar levels
25 Numbers in parentheses are numbers of mice that had coiwulsious in each dose group.

Main study

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Post-treatment, nice were continuously observed for a period of 120 minutes for incidence of clonic convulsions, as shown in the Table below

Incidence and intensity of clonic convulsions in CD-1 mice dosed intraperitoneally with Bupropion HCl or Bupropion HBr (Second study, N=10/dose group)

Mean Number of Convulsions/Mouse
Dose (mg/kg) Bupropion HIC1 Bupropion HBr
100 0 1.0(3/10)
125 16.0 (10/10) 14.3 (8/10)
150 827(10/10) 57.3(10/10)
Dose level is quoted as Bupropion HCL Bupropion HBr is administered at equimolar levels
Numbers in parentheses are numbers ofmice that had convulsions in each dose group.

10 Combined studies

15

The pooled data for the two studies for the incidence of clonic convulsions is shown in the
table below:

Incidence and intensity of clonic convulsions in CD-1 mice dosed intraperitoneally with Bupropion [IC! or Bupropion HBr (Pooled data N=13/dose group).

Mean Number of Convulsions/Mouse
Dose (mg/kg) Bupropion HCl Bupropion HBr
100 0.2(2/13) 0.8(3/13)
125 13.7(13/13) 12.8(11/13)
150 71.0 (13/13) 46.6 (13/13)
Dose level is quoted as Bupropion MCi. Bupropion HBr is administered at equimolar levels
Numbers in parentheses are numbers of mice that had convulsions in each dose group.

20 The Table below shows the pooled data for severity of clonic convulsions. Intensity of clonic convulsions in CD-1 mice dosed intraperitoneally with Bupropion
HCl or Bupropion HBr (Pooled data N=13/dose group).
Mean intensity of Convulsions/Mouse of Total
Dose (m2/k Bupronion HCl Bupropion HBr

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100
Severe 66.7 0.0
Moderate 33.3 10.0
Mild 0.0 90.0

125
Severe 71.9 47.3
Moderate 10.1 31.7
Mild 18.0 21.0

150
Severe 79.0 53.0
Moderate 12.2 25.7
Mild 8.8 21.3

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From the above results it is clear that the threshold dose for induction of clonic convulsions
5 for both salts is approximately 100mg/kg (as bupropiori HCl. At this level due to the low number of
convulsions observed per mouse it is difficult to discern meaningful differences between the two salt forms although we do observe attenuation ofthe severity ofthe convulsions with the HEr salt.
At the 125mg/kg dose level a 6.6% reduction in the mean number of convulsions per mouse
and a 15.4% reduction in the number of convulsant mice is observed. Furthermore it would seem
10 that at this level the HC1 salt has reached the top of its dose response curve whereas this is not the
case for the HEr salt. As observed at the 100mg/kg dose level the severity ofthe convulsions is also attenuated with a 34.2% reduction in the % ofsevere convulsions observed.
At the 150mg/kg dose level both salt forms are at the top oftheir dose response curves.
However the reduction in the mean number of convulsions per mouse is even more marked than at
15 the 125mg/kg dose level with a 34.4% reduction in the number of convulsions observed. Again the
severity ofthe convulsions is attenuated with a 32.9% reduction in the % ofsevere convulsions observed.

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A statistical analysis was also conducted to investigate the relative proconvulsant properties ofthe two bupropion salts: bupropion hydrochloride and bupropion hydrobromide. Post-treatment, mice were continuously observed for a period of 120 minutes for incidence
and intensity of clonic convulsions. Number of convulsions and the intensity ofthe
5 convulsions were recorded. The data is presented below.

Number of convulsions per mouse by severity (Pooled data N=13/dose group).
Dose (mg/kg) Intensity of
Convulsions

Mean Number of Convulsions/Mouse (Total Number)
Bupropion HCI (N=13) Bupropion H]3r (N13)
100 Severe 0.15 (2) 0.0(0)
100 Moderate 0,08(1) 0.08(1)
100 Mild 0.0(0) 0,69(9)
125 Severe 9.85 (128) 6.08 (79)
125 Moderate 1.38 (18) 4.08 (53)
125 Mild 2.46 (32,) 2.69 (35)
150 Severe 56.08(729) 24.69(321)
150 Moderate 8.69(113) 12.00(156)
150 Mild 6,23 (81) 9.92 (129)
Dose level is quoted as Bupropion HC1. Bupropion HBr is administered at equirnolar levels

10 Mild: Head and tail slightly extended and little jerking;
Moderate: Head and tail fully extended with some jerking;
Severe: Head and tail fully extended with strong jerking.
Statistical Analysis: Step 1: To detect general difference in. the patterns of convulsion
occurrence in terms ofintensity between the bupropion hydrochloride and bupropion
15 hydrobromide salts. The Cochran-Mantel-Haenszel test was performed and showed that the
association between the salts (bupropion hydrochloride or bupropion hydrobromide) and severity of convulsions, controlling for dose level, was statistically significant (p 0.0001).
The results indicated that, given any dose level, there was statistical evidence that the two
salts had different patterns in terms of convulsion intensities.
20 Step 2: To further investigate the patterns of convulsion occurrence using loglinear Poisson
regression models. The number of convulsions was analyzed using the loglinear Poisson regression models with formulation, dose, and severity as predictors. With the main effects

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model (the model with formulation, dose and severity main effects only), it showed that, adjusted for dose and severity, the odds of number of convulsions ofthe bupropion hydrochloride group vs the bupropion hydrobromide group is exp(0.343 6)= 1.41, or a 41% increase. This increase was statistically significant (p 0.001). Further investigations revealed
5 that there is a significant interaction term between formulation and severity (p 0.001). While
the bupropion hydrochloride group had more severe convulsions, the bupropion
hydrobromide group had more mild and moderate convulsions. The relative log number of convulsions is displayed in FIG. 26.

10 In addition, the data can also be presented as the cumulative table. In all but one case (0.23
vs 0.77, all in 100 mg/kg), the bupropion hydrochloride group had higher cumulative incidence rate of convulsions compared to the bupropion hydrobromide group. This is seen most clearly at the highest dose tested (150 mg/kg)

15 Number of convulsions per mouse by severity - Cumulative (Pooled data N13/dose group)
Dose (mg/kg) Intensity of
Convulsions

Mean Number of Convulsions/Mouse

Bupropion HCI (N=13) Bupropion HBr N=13)
100 Severe 0.15 0.0
100 Severe+
Moderate

0.23 0.08

100 All 0.23 0.77
125 Severe 9.85 6.08
125 Severe+
Moderate

11.23 10.16

125 All 13.69 12.85
150 Severe 56.08 24.69
150

150

Severe
Moderate
All

64.77

71.00

36.69

46.61

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The main study showed that higher incidence of convulsions was observed in the bupropion hydrochloride group compared to the bupropion hydrobromide group. The increase was

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around 41% on average and was statistically significant (p 0.001). Furthermore, the bupropion hydrochloride group appeared to have much more severe convulsions in proportions compared to the bupropion hydrobromide group.
In terms ofthe cumulative incidence, the raw data showed very clear trends that the
bupropion hydrochloride salt was consistently higher compared to the bupropionn,
hydrobromide salt.

EXAMPLE 6: Stability and Comparative Dissolution Studies
The stability ofBupropion HBr under various conditions and in certain embodiments ofthe
10 invention was investigated and compared with Bupropion HCl. In addition, the dissolution
profiles ofBupropion HBr XL tablets in various media were investigated. For example, the dissolution profiles ofthe 174 mg and 348mg Bupropion HBr XL tablets were measured in
the following media: 0.1 NHC1, water, acetate buffer (pH 4.5), phosphate buffer (pH 6,2), 5% ethanol in 0.1N HC1, 20% ethanol in 0.1N HC1, and 40% ethanol in 0.1NHC1. In addition, the
15 dissolution profiles ofthe 522 mg Bupropion HBr XL tablets were measured in the following
media: 0.1N HCl, 5% ethanol in 0.1N HC1, 20% ethanol in 0.1N HCl, and 40% ethanol in
0. 1NHC1.

In the following stability studies, Bupropion HBr in the form ofXL tablets were
tested as per ICH guidelines under conditions of constant temperature and humidity for
20 periods of 0, 3, 6, 9 and 12 months at 25 degrees C 4-1- 2 degrees C and 60 +7- 5 % relative
humidity (RH) and under accelerated conditions of 40 degrees C +7- 2 degrees C and 75 +1- 5
% RH which allowed for the calculation/estimation ofstability data at 18 months. The
Bupropion HBr XL tablets were stored in bulk containers (LDPE bags and fiber drums) and
in 7, 30 and 90-count HDPE bottles, The samples were exposed to controlled conditions of
25 humidity and temperature in a stability chamber.
After exposure, the tablets were tested for physical description, moisture content by Karl
Fischer, assay and impurities by 1-IPLC, and dissolution properties after 3, 6, 9 and 12
months. The dissolution test was performed by placing the test sample in 900 ml of 0.1N HCl
at 37 degrees C +1- 0.5 degrees C in an automated USP Dissolution Apparatus Type 1
30 (Basket) with stirring at 75 rpm. Samples and standard bupropion hydrobromide active were
analyzed with a UV spectrophotometer at a wavelength of 252 rim.
The Bupropion HBr XL tablets used in both the stability and dissolution studies were
prepared by granulating Bupropion HBr in a fluid bed using an aqueous solution of polyvinyl

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alcohol using top spray technology with a 0.8 mm nozzle. After granulation and drying the granules are screened through a 1.4 mm sieve and blended with glyceryl behenate lubricant
(e.g. Compritol 888 ATO) in a blender to produce a bulk blend. The bulk blend is then
pressed into tablets using a Fette2200 tablet press.
5 The tablets were then coated in a tablet coater with a coating solution prepared by mixing a
homogenized (DeBee homogenizer)mixture of dibutyl sebacate and polyethylene glycol
4000 in 190-200 proof ethyl alcohol in which has been incorporated ethylcellulose and polyvinylpynolidone (e.g. povidone) using a powder dispersion unit, and coated with carnuba

wax.

10 In-vitro dissolution experiments were performed on 174mg, 348mg and 522mg Bupropion
HBr XL tablets using USP Type 1 apparatus with a rotational speed of 75rpm, temperature of
37 degrees C – 0.5 °C, 900m1 of dissolution media, and detection at UV wavelength of
252nm. Dissolution media included 0.1N HCl (100%); Ethanol (5%) with 0.1N HCI (95%); Ethanol (20%) with 0.1N HCI (80%); and Ethanol (40%) with 0.1N HCl (60%). The
15 dissolution experiments investigated the risks of alcohol-induced dose dumping on the
noted dosage forms. Dissolution data was provided: after 2 hours for all dosage forms for 12 tablets in 0. IN HCI, 5% ethanol in 0.1 N HC1, 20% ethanol in 0.1 N HCI, and 40% ethanol in
0. 1NHCI; after 16 hours for 6 of the 522mg Bupropion HBr XL tablets in 0. 1NHC1, and 40% ethanol in 0.1N HC1; and after 20 hours for 6 ofthe 174mg and 348mg Bupropion HBr XL
20 tablets in 0.1 N HCI, and 40% ethanol in 0.1N HCI. In all cases, the dissolution profiles
showed that the release rate profile ofthe Bupropion HBr drug product was slower in the presence of alcohol (e.g. 40% ethanol) when compared with the release rate profile ofthe
same dosage form in 100% 0.1N HCI.

25 Results are shown below and in Figures 27-32, where Compound C is the intermediate bupropion degradation product 20U78, Compound E is the intermediate bupropion degradation product 827U76, and Compound F is the intermediate bupropion degradation product 852U77:

30 Bupropion HBr 174mg/348mg - Stability Data Evaluation
Condition: 25 degrees C / 60%RH;
Time Points: 0, 3, 6, 9, 12 months

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174mg

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Test Item %Change I month Total changes (%) in 18
months (as calculated)
Dissolution
2hours +0.17% +3.1%
4hours +0.13% +2.3%
8hours -0,09% -1.6%
16 hours -- --
Assay
3ChlorobenzoicAcid +0.003% +0.05%
+0.0008% +0.01%

Compound --
Compound F 0.003% +0.05%
Total Impurities 0.007% 0.13%

348mg
Test Item %Changel month Total changes (%) in 18
months (as calculated)
Dissolution
2 hours +0.12% +2.2%
4hours -- --
8 hours --
16 hours +0.06% 1.1%
Assay
3 Chlorobenzoic Acid +0.003% 0.05%
Compound C +0.001% 0.02%
Compound -- --
CompoundF +0,003% +0.05%
Total Impurities +0.007% +0.13%

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Stability Data Comparison - Bupropion 110 vs. Bupropion HBr

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The Bupropion HBr tablets (174, 348 & 522mg dosages) were in the form of XL tablets as described above. The Bupropion HO tablets (150 & 300mg dosages) were made in the same manner as the Bupropion HBr tablets. The Bupropion HC1 tablets had the same formulation
5 as the Bupropion HBr tablets with the exception that the Bupropion HO tablets had a
moisture barrier coating surrounding the controlled release coating, and a different plasticizer
in the coatings. The ingredients ofthe 2nd coat (i.e. moisture barrier coat) in the Bupropion
HC1 tablets were: Eudragit L30D 55 (film forming polymer, 24% total in 150mg tablet; 1.9% total in 300mg tablet) PEG 1450 (0.3% in 150mg, 0.25% in 300mg), silicon dioxide (0.9% in
10 150mg; 0.7% in 300mg), Triethyl citrate (0.12% in 150mg; 0097% in 300mg) The
plasticizer used in the coatings ofthe Bupropion HCl tablet was PEG1450 in the following amounts: Bupropion HCl 150mg tablet: PEG1450=1.8% total (1.5% in 1st coat; 0.3% in 2nd coat); Bupropion 1-ICI 300mg tablet: PEG1450=1.2% total (0.95% in 1st coat; 0.25% in 2nd coat), The controlled release coating ofthe Bupropion HBr tablet had a plasticizer mix of
15 dibutyl sebacate and PEG4000.

Experimental specification limits
12 months results comparison (25 degrees C 160% RH)
Assay; 90%- 110%ofLC
3 Chlorobenzoic Acid NMT 0.7%
Related Compound.0 NMT 0.3%
Related Compound E NMT 0.4%
Related Compound F NMT 1.0%
Total Impurities NMT 2.5%

Stability Data comparison at 12 months
(25 degrees C 160% RU)

Test

Bupropion HG Bupropion HBr

1501wg 300m- 174mg 348mg
Assay 94.7% 97.5% 98.3% 97.9% 3Chloroberjzoic 0.14% 0.13% 0.04% 0.04%

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Compound C 0.01% 0.02% 0.04% 0.04%

Compound 0.01% 0.02% 0.01% 0.01%

Cornpo and F 0.12% 0.11% 0.06% 0.06%
Total Impurities 0.41% 0.36% 0,26% 0.26%
Dissolution
2 hours 2.5% 3.4% 33,4% 34.6%
4 hours 26.6% 27.1% 62.2% 59.0%
8 hours 72.1% 65.5% 94.9% 91.01VO
15 hours 95.4% 93.4% 100.3% 986%

Experimental specification limits
6 mouths results comparison (25 degrees C 60% RI-1)
Assay: 90% 110% of LC
3 Chlorobenzoic Acid NMT 0.7%
Related Compound C NMT 0.3%
Related Compound E NMT 0.4%
Related Compound F NMT 1.0%
Total Impurities NMT 2.5%

Stabili Data Comparison at 6 months
(25 degrees C’60% RH)

Test

Bupropion HCl Bupropion Mir

150mg 300mg 1741ng 348mg 522mg
Assay 96.6 98.3 98.03 97.21 98.08
3-Chlorobenzoic 0.10 0.09 0.03 0.03 0.03
Related Compound C 0.02 0.02 0.02 0.02 0.04
Related Compound E 0.02 0.01 0.01 0.01 0.01
Related Compound F 0.12 0.10 0.05 0.05 0.04

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Compound C 0.00% 001% 0.04% 0.03%

Compound 0.01% 0.01% 0.01% 0,01%

Compound 0.12% 0.09% 0.05% 0,05%

Total Impurities 0.38% 0.35% 0.21% 0.21%

Dissolution

2 hours 2.3% 3.2% 32.5% 33.7%
4 hours 24.8% 26.6% 61.8% 59.2%
S hours 72,5% 67.0% 95.6% 90.4%
16 hours 95.5% 94.1% 99.8% 98.6%

Experimental specification limits
Prophetic 18 months results comparison (25 degrees C I 60% RH)
Assay: 90% 110% of LC
3 Chlorobenzoic Acid NMT 0.7%
Related Compound C NMT 0.3%
Related Compound E NMT 0.4%
Related Compound F NMT 1.0%
Total Impurities NMT 2.5%

Prophetic Stability Data Comparison as calculated at 18 months
(25 degrees C / 60% RU)
Bupropion HCI Actual Bupropion TTBr
Test Testing) (Predicted Results)
150mg 3 00m 174mg 348mg
Assay 95,7% 98.00/, 97.3% 97.9%

3 - Chlorobeiizoie 0.18% 0.16% 0.06% 0.06%

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Total Impurities 0.35 0.33 0,16 10,17 0.18
Dissolution
2 hours 2.40 3.50 32.28 33.87 32.26
4 hours 25.79 28.77 61.96 59.96 55.30
8 hours 73.88 69.47 95.87 91.72 85.09
16 hours 96.02 94.60 99.93 98.44 98.96

Dissolution data was also obtained for Bupropion 1-IC1 tablets as above (150mg and 300mg) but with the Bupropion HCI tablets having only one controlled release coating (i.e. without
5 the moisture barrier coating), as follows:
1 hour: 28-32%
2 hours: 50-55%
3 hours: 70-75%
4 hours: 85%
10 5 hours: approximately 100%
in 0.1 N HC1 using USP Apparatus I at 75 rpm and 37 – 0.5 °C.

EXAMPLE 7: BioavailabilitytPharmacokinetic (PK) Studies

15 Two-Way Crossover, Open-Label, Multiple-Dose, Fasting, Comparative Bioavailability
Study ofBupropion HBr XL 348 mg Tablets Versus Wellbutrin XLfi 300 mg Tablets in
Normal, Healthy, Non-Smoking Male and Female Subjects. Study B06-756PK-10121 (3230)

In this study the rate and extent of absorption of Bupropion HBr XL 348 mg tablets was
20 studied relative to Weilbutrin XLfi 300 mg tablets under multiple-dose fasting conditions.
The study showed that Bupropion HBr XL 348 mg tablets were equivalent to Weilbutrin
XLfi 300 mg tablets under multiple-dose fasting conditions.

25

Results are shown below and inFigures 33-37

Study Design and Phase of Development:

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Two-way crossover, randomized, steady-state, open-label, multiple-dose, fasting, relative bioavailability study.

Objectives:
5 The objective ofthis study was to compare the rate and extent of absorption of bupropion
from a novel formulation ofBupropion I-JBr XL 348 mg Tablets versus the reference Wellbutrin XLfi 300 mg Tablets at steady-state (SS) under fasting conditions.

Main Criteria for Inclusion:

10 Nonnal, healthy, non-smoking male and female subjects at ages of from 18 to 55 years.

Titration Product, Lot Number and Mode ofAdministration:
Following an overnight fast of at least 10 hours, 1 Wellbutrin XLfi 150 mg Tablet, Lot #: 05K077P, administered orally with 240 tnt of ambient temperature water on Days 1 to 3 of
15 each study period.

Test Product/Investigational Product, Batch or Lot Number and Mode of Administration: Following an overnight fast of at least 10 hours, 1 Bupropion HBr XL 348 mg Tablet, Lot #: 06C 159P (potency value = 97.0% oflabel claim), administered orally with 240 tnt of
20 ambient temperature water on Days 4 to 13 ofthe study period.

Reference Product, Batch or Lot Number and Mode ofAdministration:
Following an overnight fast of at least 10 hours, 1 Wellbutrin XLfi 300 rng Tablet, Lot #: 06C090P (potency value = 99.3%oflabel claim), administered orally with 240 niL of
25 ambient temperature water on Days 4 to 13 ofthe study period.

Number of Subjects (planned and analyzed):
There were 48 subjects dosed in Period I, 40 ofwhom completed the study. The final phannacokinetic and statistical analyses were performed on 38 ofthe 40 subjects who
30 completed the study.

Blood Draw Timepoints:

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During each study period, 19 blood samples were collected from each subject at the
following timepoints:
Days 1, 10, 11, and 12: 0.00 hour (pre-dose)
Day 13: 0.00 (pre-dose), 1.00, 2.00, 3,00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 14.00,.
5 16.00, 20.00, and 24.00 hours post-dose.
There were no blood samples taken on Days 2, 3, 4, 5, 6, 7, 8, and 9.
All pre-dose blood samples were drawn within 10 minutes before dosing.

Bioanalytical Procedure:
10 Bupropion and its metabolites, bupropion erythroamino alcohol, bupropion threoarnino
alcohol, hydroxybupropion, and the internal standard, 1 -(3-chiorophenyl)-piperazine, were extracted by solid phase extraction into an organic media from 0.50 mL of human plasma. An aliquot ofthis extract was injected into a High Performance Liquid Chromatography system
and detected using a tandem mass spectrometer. The analytes were separated by reverse
15 phase chromatography. Evaluation ofthe assay was carried out by the construction of an 8
point calibration curve (excluding zero concentration) covering the range of 1.000 ng/mL to 103.900 ng/mL for bupropion, 1.000 ng/mL to 1023.900 ng/mL for bupropion erythroamino
alcohol, 1.000 ng/mL to 1023.900 ng/mL for bupropion threoamino alcohol, and 3.906
ng/mL to 3999.600 ng/mL for hydroxybupropion in human plasma. The slope and intercept
20 ofthe calibration curves were determined through weighted linear regression analysis (1/peak
area2). Two calibration curves and duplicate QC samples (at three concentration levels) were
analyzed along with each batch ofthe study samples. Peak area ratios were used to determine Stheconcentration ofthe standards, quality control samples, and the unknown study samples from the calibration curves.
25
Criteria for Evaluation:

The pharmacokinetic analysis was performed on 38 subjects who completed the 2 study
periods. The safety assessment was performed on all subjects who received at least 1 dose
during the course ofthe study.

Pharmacokineties (PK:
The following pharmacokinetic parameters for bupropion and its metabolites hydroxybupropion, bupropion threoamino alcohol, and bupropion erythroanino alcohol were

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calculated by standard noncompaitmental methods: AUC, Cmax, Cmiii, Cavg, MRT, MYP ratio, % Fluctuation, Q/0 Swing, and Tmax. These parameters were also computed for pharmacologic activity-weighted composite (PAWC).

5 Statistical Methods:

Using General Linear Model (GLM) procedures in Statistical Analysis System (SAS),
analysis ofvariance (ANOVA) was performed on in transformed AUC, Cmax, Cmiii, Cavg,
and on untransformed MRT, MIP ratio, % Fluctuation and % Swing at the significance level
of 0.05. The intra-subject coefficient ofvariation (CV) was calculated using the Mean
10 Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90%
geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the In transformed AUC, Cmax, Cmin, between the test and reference formulations. Tmax was analyzed using nonparametric methods.

15 PHARMACOKINETIC PARAMETERS FOR BUPROPION:

Phaimacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD
Bupropion HBr XL 348 mg Weilbutrun XLfi 300 mg
Tablets (A) (n38) Tablets (B) (-n=38)
AUCtnghr/mL) 1362,44 (24.53) 1541.27 (20.43)
1409.24–345.72 1575.03–321.80

Cmax (ng/mL) (28.44) 151.03 (27.15)
134.33 38.20 156.83 42.57

Cmin (ng/mL) 24.72 (37.50) 26.95 (3148)
26.60 9.98 28.32 8.92

Cavg (ng/niL) 56.77 (24.53) 64.22 (20.43)
58.72 14.41 65.63 13.41

Tmax (hr) 4.01 (2.00 7.00) 4.50 (3.00 7.00)
Degree of Fluctuation 187.51 53.50 195.47 47.80
(%)
Degree of Swing (%) 475.44 280.21 499.74 228.53
MRT (hi’) 9.12 0.72 9.76 0.69

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median - max)

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RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION:
Parameter Potency Uncorrected Data
90% C.I. Ratio ofMeans intraSubject CV
AUCt 84.19% to 93.95% 88.93% 14.16%
Cmax 80.20% to 92.15% 85.97% 17.97%
Cniin 86.56% to 100.00% 93.04% 18.68%
Parameter Potency Corrected Data
90% C.I. Ratio ofMeans
AUCO-t 86.18% to 96.18% 91.04%
AUCO-inf 82.10% to 94.33% 88.00%
Cmax 88.61%to102.37% 95.24%

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PHARMACOKINETIC PARAMETERS FOR HYDROXYBUPROPION:

Pharmacokinetic
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD
Bupropion HBr XL 348 rng
Tablets (A) (n38)

Welibutrin XLfi 300 mg
Tablets (13) (n38)
AUCt(ng hr/niL) 21815.79 (29.60)
22879.88 6771.48

25099.08 (29.19)
26180.58 7642.05

Cmax (ngluiL) 1158.54 (28.08)
1208.14–339.24

1344.33 (29.42)
1403.10–412.83

Crnin (ng/mL) 762.55 (34.99)
814.63–285.05

895.28 (32,81)
944.00–309.69

Cavg(ng/mL) 908.99 (26.0)
953.33–282.14

1045.80 (29.19)
1090.86–318.42

Tmax (hr) 6.00 (3.00 10.00) 7.00 (4.00 - 10.02)
Degree of Fluctuation
(%)

43.46– 16.88 43.12– 17.82

Degree of Swing (%) 53.97 25.74 52.19 – 26.83
MRT(hr) 11.32–0.31 11.51–0.29
M/PRatio 15.57–4.20 15.97–4.84
median max)

RELATIVE BIOAVA]1LABILITY ASSESSMENTS FOR HYDROXYBUPROPION:

Parameter Potency Uncorrected Data
90% C.I. Ratio ofMeans Intra-Subject CV
AUCt 82.96% to 92.04% 87.39% 13.39%
Cmax 81.93% to 91.10% 86.39% 13.68%
Crnin 81.45% to 90.94% 86.06% 14.22%

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PHARMACOKINETIC PARAMETERS FOR BUPROPION THREOAMINO ALCOHOL:

Pharmacolc.ineti,c
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD

Bupropion HBr XL 348 mg
Tablets (A) (n38)

Welibutrin XLfi 300 mg
Tablets (B) (n38)
AUCt (ng hr/mL) 8842.06 (37.35)
9446.28 3528.05

9768,54 (27.53)
10112.95 2783.98

Cmax (nglrnL) 486.58 (34.68)
514.82– 178.53

541.95 (26.73)
560.74– 149.88

Cmiii (ng/mL) 282.78 (47.91)
312.46–149.70

318.60 (34.19)
335.65–114.75

Cavg ng/mL) 368.42 (37.35)
393.60 147.00

407.02 (27.53)
421.37 116.00

Tmax (hr) 6.00 (3.00 10.00) 7.00 (5.00 14.00)
Degree of Fluctuation
(%)

55.17– 18.45 55.08– 19.06

Degree of Swing (%) 74.98 32.28 72.78 31.30
MRT(Iir) 11.39–0.37 11.60–0.28
M/P Ratio 6.76 2.29 6.60 2.34

median - max)

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BIJPROPION THREOAMINO ALCOHOL:

Parameter Potency Uncorrected Data
90% C.I. Ratio ofMeans Intra-Subject CV
AUCt 85.78% to 96.23% 90.86% 14.83%
Cmax 84.49% to 95.91% 90.02% 16.38%
rnin 83.54% to 95.43% 89.29%17.21%

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PHARMACOKIETIC PARAMETERS FOR BUPROPION ERYTHROAMINO
ALCOHOL:

Pharmacokinctic Geometric Mean (%CV)
Parameters Arithmetic Mean SD

Bupropion HBr XL 348 mg Welibutrin XLfi 300 mg
Tablets (A) (nz38) Tablets (B) (n38)
AUCt (ng hr/rnL) 1922.76 (29.01) 2091.51 (22.07)
2009.09+582.74 2143.79–473.12

Crnax(ng/rnL) 99.98 (27.31) 108.26 (23,57)
103,93 28.38 111.35 26.25
Crain (ug/niL) 67.46 (35.71) 76.01 (25.97)
72.00 25.71 78.52 20.39

Caygng/mL) 80.11 (29.01) 87.15 (22.07)
83.71 24.28 89.32 19.71

Tmax (hr) 7.00 (5.00 14.00) 7.00 (5.00 12.00)
Degree ofFluctuation 40.46 16.49 37.10 14.22
(%)
Degree of Swing (%) 50.16–24.94 43.65+ 19.18
MRT(hr) 11.54+0.32 11.72–0.25
M/PRatio 1.47–0.45 1.40–0.42
rnecuan min max

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Parameter Potency Uncorrected Data -
90% C.I. (Ratio ofMeans Intra-Subect CV

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AUCt 87.32% to 97.69% 92.361M, 14.480/.
Cmax 87.66% to 97.91% 92.64% 14.27%
Cmiii 83.81% to 95.28% 89.36% 16.57%

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PHARMACOKINETIC PARAMETERS FOR TOTAL BUPROPION (PAWC):

Pharmacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD
Bu:propion HBr XL 348 mg Welibutrin XLfi 300 mg
Tablets (A) (n=38) Tablets (B) (n=38)
AUCt (M.hr) 66.48 (26.44) 75.89 (24.59)
69.03 18.25 78.13 19.21
Cmax (tiM) 3.70 (24.37) 4.26(25.37)
3.81 0.93 4.39 1,11
Cmin (M) 2,21 (32.88) 2.57 (29,67)
2.34 0.77 2.68 0.79
Cavg (M) 2.77 (26.44) 3.16 (24.59)
2.88 0.76 3.26 0.80

Tmax (hi) 5.00 (2.00 10.00) 6.00 (4.00 10.02)
Degree ofFluctuation 53.54– 17.61 53.73– 18.91
(%)
Degree of Swing (%) 69.50 29.41 68.34 30.09
MRT(br) 11.15–0.32 11.38–0.31
median - max)

RELATIVE BIOAVAILAI ILITY ASSESSMENTS FOR TOTAL BUFROPION (PAWC):
Parameter Potency Uncorrected Data
90% C.I. Ratio ofMeans Intra-Subject CV
AUCt 83.72% to 92.62% 88.06% 13.02%
Cmax 82.39% to 92.05% 87.09% 14.31%
Cmin 82.48% to 91.87% 87.05% 13.91%

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Conclusion:

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The pharmacokunetics of bupropion were assessed, after multiple oral doses ofBupropion
HBr XL 348 mg Tablets (Treatment A), and Weilbutrun XLfi 300 mg Tablets (Treatment B) under fasting conditions.

The comparative bioavailability of bupropion, its metabolites and the pharmacologic activity-weighted composite (PAWC) data were assessed by measuring and comparing the peak and total systemic exposure from the two treatments at steady state.

The statistical results indicated that steady state was achieved by Day 13. The test/reference geometric mean ratios and the corresponding 90% confidence intervals for AUCt, Cmax, and Cmiii were within the range of 80.00%-125.00% for bupropion, its metabolites and the PAWC under steady-state fasting conditions. There was no significant difference in the bupropion Tmax values between the two treatments (p value 0.05).

In conclusion, Bupropion HBr XL 348 mg Tablets demonstrated equivalent peak concentration, minimum concentration and systemic exposure relative to Wellbutrin XLfi 300 mg Tablets under steady-state fasting conditions.

Overall, Bupropion HBr XL 348 mg Tablets were well tolerated when administered under multiple-dose, fasting conditions, and no significant safety issues emerged.

This study was performed in compliance with (3CP,

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Table: Mean (–SD) Pharmacokinetic Parameters for Bupropion (n = 38) Bupropion HBr XL
348 mg Tablets
(06C159)
(n38)

Welibutrin XLfi
300 mg Tablets
(06C090P)
(n=38)
AUC0-c(ng hr/mL) 1409–346 1575–322
Cmax ngImL) 134–38 156.8 –43
Cmin (ng/mL) 26.6 10.0 28.3 – 8.9
Cavg(rg/mL) 58.7– 14.4 65,6–13.4
Trnax (hr) 4.0 (2.0 7.0) 4.5 (3.0 7.0)
Degree of
Fluctuation (%)

187.5–53.5 195.5–47.8

Median (Range)

Table: Summary Statistics for Bupropion (n = 38)

Bupropion HBr XL 348 mg Tablets
Versus Weilbutrinfi XL 300 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-’c 88.93 84.19 to 93.95
Cmax 85.97% 80.20 to 92.15 %
Crnin 93.04% 86.56 to 100.00

Table: Mean (–SD) Phaniiacokinetic Parameters for Hydroxybupropion (n = 38)
Bupropion. HBr XL Weilbatrin XLfi
348 mg Tablets 300 mg Tablets
(06C159) (06C090P)
(n=38) (n=38)
AUCO-T (ng hr/mL) 22880– 6771 261.81– 7642
Cmax(ng/mL) 1208.1 – 339.2 1403.1 –412.8

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Cmi.n (ng/mL) 814.6 285.1 944.0 309.7
Cavg (nglrnL) 953.3 282.1 1090.9 318.4
Tmax (hr) 6.0 (3.0 10.0) 7.0 (4.0- 10.0)
Degree of Fluctuation
(%)

43.5 16.9 43.1 17.8

Metabolite/ Parent
Ratio

15.6 4.2 16.0 4,8

Median (Range)

Table Summary Statistics for Hydroxybupropion n = 38)

Bupropion HBr XL 348 rug Tablets
Versus Weilbatrinfi XL 300 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-t 87.39% 82.96 to 92.04
Cmax 86.39% 81.93 to 9 1.10 %

r-CTTi77- 86.06% 81.45to90.94%

Table: Mean (–SD) Pharmacokinetic Parameters for Bupropion Threoamino Alcohol n 38)

S Bupropion HBr XL
348 mg Tablets
(06C159),
(n=38)

Welibutrin XLfi
300 mg Tablets
(06C090P)
(n38)
AUC0-(ng hr/mL) 9446+3528 10113 –2784
Cmax (ng/mL) 514.8 178.5 560.7 149.9
Cmin(ng/mL) 31,2.5– 149.7 335.7+ 114.8
Cavg(ng/mL) 393.6+147.0 421.4–116.0
Tmax (hr) 6.0 (3.0 10.0) 7.0 (5.0 14.0)
Degree ofFluctuation 55.2 18.5 55.1 19.1

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Metabolite/ Parent
Ratio

6.8–2,3 6.6–2.3

Median (Range)

Table: Summary Statistics for Bupropion Threoarnino Alcohol (n 38)

Bupropion HBr XL 348 mg Tablets
Versus Weilbutrinfi XL 300 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
interval
ATJCO-t 90.86% 85,78 to 96.23
Cmax 90.02% 84.49 to 95.91
Cmin 89.29% 83.54 to 95.43

Table: Mean (–SD) Pharmacokinetic Parameters for Bupropion Erythroamino Alcohol n = 38)
Bupropion HBr XL
348 mg Tablets
(06C159)
(n=38)

Weilbutrin XLfi
300 mg Tablets
(06C090P)
(n38)
AUC0-c(ng hr/mL) 2009–583 2144–473
Crnaxg!mL) 103.9–28.4 111.4–26.3
Cmin(ng/mL) 72.0–25.7 78.5–20.4
Cavg (ng/mL) 83.7 24.3 89.3 19.7
Trnax (hr) 7.0 (5.0 14.0) 7.0 (5.0 12.0)
Degree of Fluctuation
(%)

40.5 16.5 37.1 14.2

Metabolite/Parent 1.5 0.5 1.4 0.4

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Median

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Table: Summary Statistics for Bupropion Erythroamino Alcohol (u = 38)

Bupropion HBr XL 348 mg Tablets
Versus Welibutrinfi XL 300 mg Tablets

Ratio bf Geometric
Means

90 Geometric Confidence
Interval
AUCO-z 92.36% 87.32 to 97.69
Cmax 92.64% 87.66 to 97.91 %
Cmin 89.36 83.81 to 95,28

Table Mean (–SD) Pharmacokinetic Parameters for PAWC (n = 38)

Pharmacokinetic
Parameters

Bupropion HBr XL
348 mg Tablets
(06C 159)
(n38)

Weilbutrin XLfi
300 mg Tablets
(06C090P)
(n38)
AUC0-(M hr) 69.0–18.3 78.1– 19.2
Cmax M) 3.8 – 0.9 4.4 – 1.1
Cmiii. M) 2.3 – 0.8 2.7 – 0.8
Cavg M) 2.9 – 0.8 3.3 – 0.8
Tmax (lit) 5.0 (2.0 10.0) 6.0 (4.0 10.0)
Degree of
Fluctuation (%)

53.5 –17.6 53.7 18.9

Median (Range)

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Table: Sununary Statistics for PAWC (n = 38)

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Bupropion HBr XL 348 mg Tablets
Versus Weilbutrinfi XL 300 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
Interval
ATJCD- 88.06% 83.72% to 92.62%
Cmax 8709% 82.39% to 92.05%

miii - i87.05% 77 82.48%to 91.87%

0 - Two-Way Crossover, Open-Label, Single-Dose, Fasting, Dosage Strength Proportionality
Study ofTwo Strengths ofBupropion HBr XL Tablets (2 x 174 mg Versus 1 x 348 mg)hn
5 Normal, Healthy, Non Smoking Male And Female Subjects. Study J306-755PK-10121 (3228)

In this study the dosage strength proportionality between the 174 mg and 348 mg strengths of
Bupropion HBr XL tablets were evaluated under single dose fasting conditions. Bupropion
HBr XL 174 mg tablets when given as 2 x 174 rng were equivalent to Bupropion HBr XL
10 348 mg tablets given as 1 x 348 mg.

Results are shown below and in Figures 38-43.

Study Design and Phase ofDevelopment:
15 Two-way crossover, randomized, open-label, single-dose, fasting, dosage strength
proportionality study

Main Criteria for Inclusion:

Normal, healthy, non-smoking male and female subjects at ages offrom 18 to 55 years.
20

Treatment A: Test Product/Investigational Product, Lot Number and Mode of Administration:

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Following an overnight fast of at least 10 hours, 2 Bupropion HBr XL 174mg Tablets, Lot #: 06D029P (potency value = 97.1% of label claim), administered orally with 240 mL of
ambient temperature water.

5 Treatment B: Test Product, Lot Number and Mode of Administration:
Following an overnight fast of at least 10 hours, 1 Bupropion HBr XL 348 mg Tablet, Lot #:
06C 159P (potency value = 97.0% of label claim, administered orally with 240 mL of
ambient temperature water.

10 Number of Subjects (planned and analyzed):
There were 48 subjects dosed in Period I, 46 of whom completed the study. Pharmacokinetic

ID and statistical analyses were performed on 46 subjects who completed the study.

Blood Draw Timepoints:
15 During each study period, 22 blood samples were collected from each subject at the
following timepoints: 0.00 (pre-dose), 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00,
12.00, 14.00, 16.00, 20.00, 24.00, 36.00, 48.00, 60.00, 72.00, 120.00, 168.00, and 216.00
hours post-dose,

20 Bioanalytical Procedure:
Bupropion, bupropion erythroamino alcohol, bupropion threoamino alcohol,
hydroxybupropion, and the internal standard, 1 -(3-chloropheny1)-piperazine, were extracted
. by solid phase extraction into organic media from 0.50 mL of human plasma. An aliquot of
this extract was injected into a High Performance Liquid Chromatography system and
25 detected using a tandem mass spectrometer. The analytes were separated by reverse phase
chromatography. Evaluation ofthe assay was carried out by the construction of an eight (8)
point calibration curve (excluding zero concentration) covering the range of 1.000 ng/mL to
1023.900 ng/mL (in human plasma) for bupropion, 1.000 ng/mL to 1023.900 ng/mL (in
human plasma) for bupropion erythroamino alcohol, 1.000 ng/mL to 1023.900 ng/mL (in
30 human plasma) for bupropion threoaniino alcohol, and 3.906 ng/mL to 3999.600 ng/mL (in
human plasma) for hydroxybupropion. The slope and intercept ofthe calibration curves were determined through weighted linear regression analysis (1/peak area2). Two calibration
curves and duplicate QC samples (at three concentration levels) were analyzed along with

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each batch of the study samples. Peak area ratios were used to determine the concentration of the standards, quality control samples, and the miknown study samples from the calibration

curves.

Criteria for Evaluation:
The pharrnacokinetic analysis was performed on 46 subjects who completed the 2 study
periods. The safety assessment was performed on all subjects who received at least 1 dose
during the course of the study.

10 Pharmacokinetics (PK:
The following pharmacokinetic parameters for bupropion and its metabolites hydroxybupropion, bupropion threoarnino alcohol, bupropion erythroamino alcohol and pharmacologic activity-weighted composite (PAWC) were calculated by standard non-compartmental methods: AUCO-t, AUCO-inf, Cmax, Tmax, Kel, t, mean residence time
15 (MRT), and Metabolite / Parent (M/P) ratio.

Safety:
The incidences of all adverse events (AEs) were tabulated by treatment and subject number. Absolute values for vital signs, electrocardiogram (ECG) parameters, laboratory parameters
20 and physical examinations were also documented and values outside the normal range were
flagged. Shifts from baseline values were tabulated. AEs were documented using.
investigator and Medical Dictionary for Regulatory Activities (MedDRA) terms.

Statistical Methods:

25 Using General Linear Model (GLM) procedures in Statistical Analysis System (SAS),
analysis ofvariance (AOVA) was performed on in-transformed AUCO-t, AUCO-inf, and Cmax and on untransformed Kel, t, MRT, and M/P ratio at the significance level of 0.05.
The intra-subject coefficient ofvariation (CV) was calculated using the Mean Square Error (MSE) from the AN OVA table. The ratio of geometric means and the 90% geometric
30 confidence interval (90% CI) were calculated based on the difference in the Least Squares
Means ofthe in-transformed AIJCO-t, AUCO-inf, and Cmax between the test and reference formulations. Tmax was analyzed using nonparametric methods.

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PHARMACOKINETJC PARAMETERS FOR BUPROPION:

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Pharmacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD
2 x Bupropion HBr XL 174 1 x Bupropion HBr XL 348
mg Tablets (A) (n46) mg Tablet (B) (n46)
AUCO-t (ng hr/mL) 1523.91 (30.65) 1493.80 (34.76)
1596.96 489.42 1581.85 549.92

AUCO-inf(ng hr/mL) 1585.29 (30.09) 1556.42 (34.03)
1658.90 499.09 1644.75 1559.69

Crnax(ng/mL) 122.81 (32.48) 132.51 (37.22)
128.54 141.75 141.16 52.54
Tmax (hr) 5.00 (3.00-6.07) 5.00 (3.00-7.00)
t (he) 23.65 7,36 23.84 6.90
Kel (hr-1) 3:29E02 1.28E-02 3.17E-02 9.78E-03
MRT(hr) 23.02–5.21 22.52–5.12
median min max)

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION:

Parameter Potency Uncorrected Data
90% C.I. Ratio ofMeans Intra-Subject CV
AUCO-t 96.48% to 107.86% 102.02% 16.01%
ATJCO-inf 96.59% to 107.41% 101.85% 15.24%
Cmax 86.68% to 99.10% 92.68% 19.29%
Parameter Potency Corrected Data
90% C.I. Ratio ofMeans
ATJCO-t 96.39% to 107.75% 101.91%
AUCO-inf 96.49% to 107.30% 101.75%
Cmax 86.59% to 98.99% 92.58%

PHARMACOKINETIC PARAMETERS FOR HYDROXYBUPROPION:

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Pharniacokinetic
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD
2 x Bupropion HBr XL 174
mg Tablets (A) (n=46)

1 x Bupropion HBr XL 348
mg Tablet (B) (n46)

AUCO-t(nghr/mL) 21175.12 (50.57)
24691,89::[- 12487,03

20088.61 (60.27)
24435.37 14728.10

AUCO-inf(ng hr/mL) 21601.69 (50.27)
25050.12 12593.05

20505.06 (59.96)
24779.61 14857.90

Cmax(ng/xnL) 421.40 (46.88)
480.18+225.10

411.57 (50.75)
478.90+243.02

Tmax (hr) 14.00 (5.00-24.00) 8.00 (5.00-24.00)
t (hr) 26.51 5.77 26.05 6.24
Kel (hr-1) 2.75E-02 6.70E-03 2.83E-02 7.62E-03
MRT(hr) 43.58–8.67 42.84–9.32
M/PRatio 15.02–9.00 15.08–11.14
median (mm - max)

RELATIVE BIOAVAILADILITY ASSESSMENTS FOR HYDROXYBUPROP1ON:
Parameter 90% C.I. Ratio ofMeans Intra-Subject CV
AUCO-t 98.60% to 112.69% 105.41% 19.23%
AIJCO-inf 98.62% to 112.54% 105.35% 19.01%
Cmax 97.00% to 108.08% 102.39% 15.53%

PHARMACOKINETIC PARAMETERS FOR B1JPROPION THREOAMINO ALCOHOL:
Pharrnacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD

2 x Bupropion HBr XL 174 1 x Bupropion HBr XL 348
mg Tablets (A) (n=46) mg Tablet (B) (u=46)
AUCO-t (ng hr/mL) 8720.28 (58.03) 8399.01 (53.61)
9894.97–5741,81 9441.77–5061.45

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AUC0-infng hr/rnL) 9433.66 (59.13)
10815.80–6395.02

9012.38 (54.93)
10252,40–5631.37
Cmax ngImL) 157.76 (45.91)
171,83 – 78.89

161.36 (40.12)
173.35 – 69.55

Tmax (hi) 8.00 (5.00-24.00) 6.00 (5.00-24.00)
t (hr) 56.77–20.15 53.97–17.31
Kel (hr-1) 1.35E-02:!L 4.44E-.03 .1.41E-02 – 4.58E-03
MRT(hr) 76.90–28.13 73.60–23.99
M/P Ratio 6.65 – 4,37 6.43 3.94
median - max)

RELATIVE I3IOAVAILABILITY ASSESSMENTS FOR BUPROPION THREOAMINO ALCOHOL:

Parameter 90% C.I. Ratio ofMeans lntra-Subject CV
AUCO-t 98.45% to 109.49% 103.83% 15.26%
AUCO-inf 99.20%to110.45% 104.67% 15.42%
Cmax 91.39% to 104.59% 97.77% 19.42%

PHARMACOKINETIC PARAMETERS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Pharmacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD
2 x Bupropion HBr XL 174 1 x Bupropion HBr XL 348
mg Tablets (A) (n46) mg Tablet (B) (n46)
AUCO-t (ng hr/mL) 1624.49 (47.41) 1556.84 (45.13)
1774.20 – 841.09 1699.49 – 767:04

AUC0-infng hr/mL) 1713.80 (46.12) 1663.28 (43.67)
1864.11 859.71 1804.53 788.09
Cmax (ng/mL) 29.54 (33.12) 29.01 (33.02)
30.79 – 10.20 30.40 – 10.04

Trnax (hr) 14.00 (5.00-24.00) 13.00 (5.00-24.00)

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t (hr). 32.71 7.84 32.51 8.78
Kel (hr-1)2.24E-02 5.24E-03 2.27E-02 5.72E-03
MRT (hr) 52.66 11.42 52.28 +12.78
M/PRatio 1.16–0.68 1.13–0.50
median (mm - max)

RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION ERYTHROAMINO ALCOHOL:

Parameter 90% C.I. Ratio ofMeans Intra-Subject CV
ATJCO-t 98.39% to 110.66% 104.35% 16.89%
AUCO-inf 97.25% to 109.16% 103.04% 16.60°7
Cmax 96.15% to 107.82% 101.82% 16,46%

PHARMACOK1NETIC PARAMETERS FOR PAWC:
Pharmacokinetic
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD
2 x Bupropion HBr XL 174
mg Tablets (A) (n=46)

1 xBupropion HBr XL 348
mg Tablet (B) (n46)
AUCO-t (M.hr) 68.99 (39.40)
74.85 29.49

66.21 (47.37)
73.65 34.89

AUCO-inf (tM.hr) 69.68 (39.62)
75.63 29.96

66.93 (47.56)
74,47 35.42
Cmax (AM) 1.60 (32.21)
1.68 0.54

1.64 (36.18)
1.76 0.64

Tmax (hr) 5.03 (4.00-14.00) 5.00 (4.00-24.00)
I (hr) 29.45 7.47 29.25 8.04
Kel (hr-1) 2.55E-02 8.61E-03 2.56E-02 7.53E-03
MRT (hr) 44.38 8.96 43.99 9.89
median - max)

10 RELATIVE BIOAVAILABILITY ASSESSMENTS FOR PAWC:

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Parameter 90% C.I. Ratio ofMeans Infra-Subject CV
AUCO-t 98.43% to 110.30% 104.20% 16.36%
AUCO-inf 98.32% to 110.25% 104.12% 16.45%
Cmax 91.74% to 102.73% 97,08% 16.26%

Conclusion:

The objective ofthis study was to evaluate the dosage strength proportionality ofthe two strengths ofBupropion HBr XL Tablets (2 x 174 mg versus 1 x 348 mg) in normal healthy non-smoking male and female subjects. The relative bioavailabiity of bupropion, its metabolites and the PAWC data were assessed by measuring and comparing the peak and total systemic exposure from the 2 treatments (using ATJCO-t, A1JC0inf, and Cmax).The statistical results indicated that test/reference geometric mean ratios and the valued of 90% confidence intervals for AUCO-t, AUCO-inf and Cmax of bupropion, its metabolites and PAW, C data were within the criteria range of 80.00% - 125.00%. Based on these results, Bupropion HBr XL Tablets (2 x 174 mg) and Bupropion HBr XL Tablets (1 x 348 mg) were found to demonstrate equivalent-peak and systemic exposure of bupropion and its metabolites when both formulations were administered under fasting condition. In conclusion, Bupropion XL 174 mg Tablets (given as 2x174 mg) were found to be dosage strength proportional to Bupropion HBr XL 348 mg Tablets. Overall, Bupropion HBr XL 174 mg Tablets (2 x 174 mg) and Bupropion HBr XL 348 mg Tablets were well tolerated as a single-dose of 348 mg, administered under fasting conditions, and no significant safety issues emerged.

This study was performed in compliance with GCP.

Table: Mean (–SD) Pharmacokinetic Parameters for Bupropion (n = 46)
2x Bupropion lx Bupropion
HBr XL HBr XL

174 mg Tablets 348 mg Tablet
(06D029P) (06C159P)
(n=46) (n=46)
AUCO-t 1597–489 1582–550
(ng hr/ml)

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AUCO-

(ng hr/mL)

1659–499 1645–560

Cmax(ng/niL) 128.5–41.8 141.2–52.5
Tmax(hr) 5.0(3.0-6.1) 5.0(3.0-7.0)
t (br) 23.7 7.4 23.8-+-6.9
MRT(hr) 23.0–5,2 22.5–5.1
Median (Range)

Table Summary Statistics for Bupropion (n = 46)

2 x Bupropion HBr XL 174 mg Tablets
Versus lx Bupropion HBr XL 348 mg Tablet

Ratio ofGeometric
Means

90 Geometric Confidence
Interval
AUCO-t 102.02% 96.48 to 107.86
AUCO- 101.85% 96,59to107.41%
Cmax 92.68% 86.68to99.10%

5 Table Mean (–SD) Pharmacokinetic Parameters for Bydroxybupropion (n =.46) 2x Bupropion
HBr XL

174 mg Tablets
(06D029P)
(n=46)

lx Bupropion
HBr XL

348 mg Tablet
(06C159P)
(n=46)
AUCO-t (ng hr/mL) 24692 –12487 24435 –14728
AUCO- (ng hr/mL) 25050–12593 24780– 14858
Crnax(ng/thL) 480.2–225.1 478.9–243.0
Tmax (hr) 14.0 (5.0 24.0) 8.0 (5.0 24.0)
t (hr) 26.5–5.8 26.1–6.2
MRT(hr) 43.6–8.7 42.8–9.3

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Metabolite/ Parent 15.0 9.0 15.1 11.1
Ratio

Median (Range)
Table: Summary Statistics for Hydroxybupropion (n = 46)

2 x Bupropion HBr XL 174 mg Tablets
Versus lx Bupropion HBr XL 348 mg Tablet

Ratio of Geometric
Means

90 Geometric Confidence
interval
AUCO-t 105.41 98.60 to 112,69
AUCO- 105,35 98.62 to 112.54%

rCmaT-- 1102,39% 97.00 to 108.08

Table. Mean (–SD) Pharmacokinetic Parameters for Bupropion Threoamino Alcohol (n 46)
2x Bupropion
HBrXL

174 mg Tablets
(06D029P)
(n=46)

ix Bupropion
HBrXL

348 mg Tablet
(06C159P)
(n=46)
AUCO-t(ng hr/niL) 9895 –5742 9442 –5061
AUCO- ng hr/niL) 10816–6395 10252–5631
Cmax(ng/tiiL) 171.8–78.9 173.4–69.6
Tmax(hr) 8.0(5.0-24.0) 6.0(5.0-24.0)
t (hr) 56.8 20.2 54.0 – 17.3
MRT(hr) 76.9–28.1 73.6–24.0
Metabolite/ Parent
Ratio

6.7–4.4 6.4 –3.9

Median (Range)

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Table Summary Statistics for Bupropion Threoamino Alcohol (n = 46)

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2 x Bupropion HBr XL 174 mg Tablets
Versus lx Bupropion HBr XL 348 mg Tablet

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-t 103.83% 98.45% to 109.49%
AUCO- 104,67% 99.20% to 110.45%
Cmax 97.77% 91.39% to 104.59%

Table Mean (–SD) Phaimacokinetic Parameters for Bupropion Erythroamino Alcohol (n
5 46)

10

2x Bupropion
HBr XL

174 mg Tablets
(06D029P)
(n=46)

lx Bupropion
HBr XL

348 mg Tablet
(06C159P)
. (n=46)
ATJCO-t(ng hr/mL) 1774–841 1699–767
AUCO- (ng hr/mL) 1864–860 1805–788
Cmaxng/mL) 30.8–10.2 30.4–10.0
Tmx (hr) 14.0 (5.0 - 24.0) 13.0 (5.0 - 24.0)
t (hr) 32.7 – 7.8 32.5 8.8
MRT (hr) 52.7–11.4 52.3 12.8
Metabolite/ Parent
Ratio

1.2–0.7 1.1–0.5

Median (Range)

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Table: Summary Statistics for Bupropion Eiythroamino Alcohol (n = 46)

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2 x Bupropion HBr XL 174 mg Tablets
Versus lx Bupropion HBr XL 348 rn.g Tablet

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-t. 104.35% 98.39% to 110.66%
AUCO- 103,04% 97.25% to 109.16%
Cmax 101.82% 96.15% to 107.82%

Table: Mean (–SD) Pharmacokinetic Parameters for PAWC n 46)
2x Bupropion lx Bupropion
HBr XL HBr XL
Pharmacokrnetic

174 mg Tablets 348 mg Tablet
Parameters

(06D029P) (06C159P)
(n=46) (n=46)
AUCO-t(M hr) 74.9+29.5 737+349
AUCO- (tM hr) 75.6 30.0 74.5 35.4
Cmax(tM) 1.7–0.5 1.8–0.6
Tmax(hr) 5.0(4.0- 14.0) 5.0 (4.0-24.0)
t (hr) 295–7.5 29.3+8.0

MRT (hr) TT.47–7-1.0 T44.0 9.9
Median (Range)
Table: Summary Statistics for PAWC (n = 46)

2 x Bupropion HBr XL 174 mg Tablets
Versus lx Bupropion HBr XL 348 mg Tablet

Ratio of Geometric 90 Geometric Confidence
Means Interval
AUCO-t 104.20% 98.43 to 110.30%

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AUCO- 104.12% 198.32t0110.25% Cmax 97,08% [91.74to102.73%

Two-Way Crossover, Open-Label, Single-Dose, Food-Effect Study ofBupropion HBr XL
348 mg Tablets In Normal, Healthy, Non-Smoking Male And Female Subjects. Study B06-754PK-10121 (3229)

The effect offood on Bupropion HBr XL 348 mg tablets was studied. Administration of Bupropion HBr XL 348 mg tablets with food resulted in an increase in the peak (Cmax) and systemic exposure (AUCO-t, AUCO-oo) ofbupropion by 7 % and 19 %, respectively. The presence offood did not change lead to a significant change in Tmax. The increase in Cmax
10 was found not to be significant since the 90 % geometric confidence interval (CI) fell within
the 80 to 125 % range. The 90 % geometric CIs for AUCO-t and AUC0-cx were found to fall slightly outside the 80 to 125 % range (90 % CIs for ATJCO-t = 113.23 to 126.06 %, for AUCO-oo = 112.96 to 125.52 %). This marginal increase in bupropionAUC with food
relative to fasting will not pose any clinical safety concerns since the percentage increase was
15 within –20 % and the upper limit ofthe 90 % geometric CI was approximately 1 % above the
acceptance range.

Results are shown below and in Figures 44-49.

20 Study Design and Phase ofDevelopment:
Two-way crossover, randomized, open-label, single-dose, food-effect, Phase I study

Main Criteria for Inclusion:

Normal, healthy, non-smoking male and female subjects within the age range of 18 to 55
25 years.

Test Product/Investigational Product, Batch or Lot Number and Mode of Administration: Following an overnight fast of at least 10 hours, and 30 minutes after the start of a high fat content meal, 1 Bupropion HBr XL 348 mg Tablet, Lot #: 06C159?, administered orally with
30 240 mL of ambient temperature water.

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Reference Product, Batch or Lot Number and Mode of Administration:
Following an overnight fast of at least 10 hours, I Bupropion HBr XL 348 mg Tablet, Lot #: 06C15 9P, administered orally with 240 mL of ambient temperature water.

5 Number of Subjects (planned and analyzed):
There were 48 subjects dosed in Period I. All subjects completed the study, and their data
were used for the pharmacokinetic and statistical analyses.

Blood Draw Timepoints:
10 During each study period, 22 blood samples were collected from each subject at the
following timepoints: 0.00 (pre-dose), 1.00, 2.00, 3,00, 4.00, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 14.00, 16.00, 20.00, 24.00, 36.00, 48.00, 60.00, 72.00, 120.00, 168.00, and 216.00 hours post-dose.

15 Bioanaiytical Procedure:
Bupropion, bupropion erythroamino alcohol, bupropion thrQamino alcohol,
hydroxybupropion, and. the internal standard, 1 -(3-chlorophenyl)-piperazine, were extracted
by solid phase extraction into organic media from 0.50 mL of human plasma. An aliquot of
this extract was injected into a High Performance Liquid Chromatography system and
20 detected using a tandem mass spectrometer. The analytes were separated by reverse phase
chromatography. Evaluation ofthe assay was carried out by the construction of an eight (8) point calibration curve (excluding zero concentration) covering the range of 1.000 ng/mL to 1023.900 ng/mL (in human plasma) for bupropion, 1.000 ng/mL to 1023.900 ng/mL (in
human plasma) for bupropion ehroarnino alcohol, 1.000 ng/mL to 1023.900 nWmL (in
25 human plasma) for bupropion threoamino alcohol, and 3.906 ng/mL to 3999.600 ng/mL (in
human plasma) for hydroxybupropion. The slope and intercept ofthe calibration curves were determined through weighted linear regression analysis (1/peak area2). Two calibration
curves and duplicate QC samples (at three concentration levels) were analyzed along with
each batch ofthe study samples. Peak area ratios were used to determine the concentration of
30 the standards, quality control samples, and the unknown study samples from the calibration

curves.

Criteria for Evaluation:

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The pharmacokinetic analysis was performed on 48 subjects who completed the 2 study periods. The safety assessment was performed on all subjects who received at least 1 dose during the course ofthe study.

5 Pharmacokinetics (PK:

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The following pharmacokinetic parameters for bupropion and its metabolites
hydroxybupropion, bupropion threoamino alcohol, bupropion erythroamino alcohol and
PAWC were calculated by standard non-compartmental methods: AUCO-t, AUCO-in– Cmax
Tmax, Kel, t, MRT, and M/P ratio.

Statistical Methods:

SUsing General Linear Model (GLM) procedures in Statistical Analysis System (SAS), analysis of variance (ANOVA) was performed on in transformed AUC0t, AUCO-inf, and
Cmax and on untransformed Kel, t, MRT, and M!P ratio at the significance level of 0.05.
15 The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error

PIC

(MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric
confidence interval (90% CI.) were calculated based on the difference in the Least Squares Means ofthe in transformed AUCO-t, AUCO-in– and Cmax between the test and reference formulations. Tmax was analyzed using nonparametric methods.

Sununary of Pharmacokinetic Results:
PHARMACOKINETIC PARAMETERS FOR BUPROPION:

Pharmacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD
Bupropion ’HBr XL 348 rng Bupropion I-Ir XL 348 mg
Tablets (A.) (Fed) (n=48) Tablets (B) (Fasted) (n48)
AUCO-t 1743.38 (29.91) 1459.22 (27.36)
(nghr/mL) 1813.67–542.56 1514.68–414.40
AUCO-iuf 1806.08 (29.34) 1516.77 (26.77)
(nghrlmt) 1876.44–550.60 1572.10–420.91
Cmax 130.36 (31.47) 121.28 (27.41)
(ng/mL) 136.80–43.05 125.91–34.52
Tmax (hr) 5.00 (2.00-10.00) 5.00 (3.00-7.00)

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t1/2 (hr) 23.19+6,45 21.29–6.65
Kel (hr-1) 3.27E-02 1.1OE-02 3.60E-02 1.171E-02
MRT(lir) 22.36+5.92 21.20–5.56
median min - max)
(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION:
Parameter 90% C.I. Ratio ofMeans Intra-Subject CV
AUCO-t 113.23% to 126.06% 119.47% 15.75%
AUCO-inf 112.96% to 125.52% 119.07% 1547%
Cmax 9820% to 117.64% 107.48% 26.83%

5 PHARMACOKINETIC PARAMETERS FOR HYDROXYBUPROPION: Pharrnacokinetic
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD
Bupropion HBr XL 348 mg
Tablets (A) (Fed) (n=48)

Bupropion HBr XL 348 mg
Tablets (B) (Fasted) (n=48)
AUCO-t

(ng h.r/mL)

21556.18 (54.71)
25505.66 + 13953.00

21143.44 (53.45)
24948.49 13334.10
AUCO-inf
(nghr/mL)

22061.74 (54.24)
25870.62– 14032.96

21628.02 (52.78)
25284.90– 13346.59
Cmax

(nglmL)

457.15 (45.58)
525.08–239.34

445.93 (43.57)
507.42–221.07

Tmax (hi’) 14.00 (7.00-36.00) 8.00 (5.00-24.02)
tl/2 (hr) 24.77 – 4.81 24.28 – 4.92
Kel (hr-1) 2.90E-02 5.59E-03 2.97E-02 5.93E-03
MRT (hr) 42.65 – 7.61 41.13 + 7.37
M/PRatio 13.17–5.96 15.48–7.32

median(min - max)

(FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR HYDROXYBtJPROPION:

Parameter 90% C.I. Ratio ofMeans 1Intra Subject CV

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AUCO-t 95.40% to 108.96% 101.95% 19.58%
ATJCO-inf 95.50% to 108,95% 102.01% 19.41%
Cmax 96.75% to 108.62% 102.52% 17.00%

PHARMACOKINETIC PARAMETERS FOR BUPROPION THREOAMINO ALCOHOL: Pharmacokinetic
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD

Bupropion HBr XL 348 mg
Tablets (A) (Fed) (n48)

Bupropion HBr XL 348 mg
Tablets (B) (Fasted) n=48)
AUCO-t

ng hrlrnL)

9430.21 (53.90)
10454.75 – 5635.07

8355.97 (53.13)
9356.36 4971.39
ATJCO-inf

(ug hr/mL)

9970.03 (54.94)
11148.70 – 6124.76

8875.08 (55.60)
10081.16 – 5604.76
Cmax

(ng/rnL)

179.62 (43.15)
193.84+83.63

154.88 (41.45)
168.36–69.79

Tmax (hr) 11.00 (5.00-36.00) 7.00 (5.00-24.00)
tl/2 (hr) 50.49 15.20 50.82 – 18.50
Kel (hr- 1) 1.49E-02 4.29E-03 1.51E-02 4.44E-03
MRT (hr) 69.31 20.00 7003 23.78
M/PRatio 5.94–2.85 6.35–3.21
meaian (mm - max)

At 5 (FED/FASTING) RELATIVE BIOAVAILABILITY ASSESSMENTS FOR BUPROPION

THREOAMINO ALCOHOL:

Parameter 90% C.I. Ratio ofMeans Intra-Subject CV
AUCO-t 106.31%to 119.80% 112.86% 17.56%
AUCO-inf 105.67% to 119.42% 112.34% 17.99%
Cmax 107.44% to 125.18% 115.97% 22.58%

PHARMACOKINETIC PARAMETERS FOR BUPROPION ERYTHROAMINO
10 ALCOHOL:

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Pharmacokinctic
Parameters

Geometric Mean (%CV)
Arithmetic Mean SD

Bupropion HEr XL 348 mg
Tablets (A) (Fed) (n48)

Bupropion HBr XL 348 mg
Tablets (B) (Fasted) (n48)
AUCO-t

(ng hr/mL)

1827.80 (41.59)
1976.58 + 822.09

1602.42 (43.32)
1762,94 763.75
AIJCO-inf

(ng hr/mL)

1922.92 (40.33)
2069.294: 834.50

1701.69 (41.91)
1860.34 – 779.59
Cmax

(ng/mL)

33.52 (29.90)
34.90–10.44

28:94 (29.09)
30.18+8.78

Tmax (hr) 14.00 (8.00-36.00) 14.00 (5.0036.00)
tl/2(hr) 31.81+7.32 31.09–7.84
Kel (hr-1)2.28E-02 4.82E-03 2.36E-02 5.60E-03
MRT(hr) 53.31+11.39 51.58+11.29
M/PRatio 1.11–0.38 1.18–0.42

median - max)

(FED/FASTING) RELATIVE BIOAVAJLABILITY ASSESSMENTS FOR BUPROPION ERYTHROAM1NO ALCOHOL:

Parameter 90% C.I. Ratio ofMeans Intra-Subject CV
AIJCO-t 106.29% to 122.40% 114.07% 20.81%
ATJCO-inf 105.83% to 120.66% 113.00% 19.32%
Cmax 108.36% to 123.83% 115.84% 19.66%

PHARMACOKINETIC PARAMETERS FOR PAWC:

Pharmacokinetic Geometric Mean (%CV)
Parameters Arithmetic Mean SD
Bupropion HBr XL 348 mg Bupropion HEr XL 348 mg
Tablets (A) (Fed) (n48) Tablets (B) (Fasted) (n48)
AUCO-t 71.68 (45.24) 68.31 (44.26)

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(pM.hr) 78.53 35.52 74.80 33.11
AUCO-inf
(iM.hr)

72.09 (45.62)
79.05 36,07

68.78 (44.28)
75.31 33.34
Cmax

(M)

1.65 (34,28)
1.75+0.60

1.67 (31-70)
1.75–0.55

Tmax (hi) 10.00 (2.00-24.00) 5.51 (4.00-24.00)
ti/2 (lit) 26.39 6.17 26.33 7.38
Kel (hr-1)2.78E-02 6.83E-03 2.81E-02 6.72E-03
MRT(hr) 42.31–7.70 41.45–8.44
median (min - max)

(FED/FASTING) RELATIVE B1OAVAILABILITY ASSESSMENTS FOR PAWC:
Parameter 90% C.I. Ratio ofMeans Intra-Subject CV
AUCO-t 98.67% to 111.60% 104.94% 18.11%
AUCO-inf 98.47% to 111.56% 104.81% 18.36%
Cmax 92.74% to 105.44% 98.89% 18.89%

Conclusion:

The objective ofthis study was to evaluate the effect of food on the rate and extent of absorption of bupropion from a novel formulation ofBupropion HBr XL (extended release) 348 mg Tablets.

The relative bioavailability of bupropion, its metabolites and the pharmacologic activity-weighted composite (PAWC) data were assessed by measuring and comparing the peak and total systemic exposure from the 2 treatments (using AUCO-t, AUCO-inf, and Cmax).

Relative to drug administration under fasting conditions, the peak and systemic exposure for bupropion following a single oral dose ofBupropion HBr XL 348 mg Tablet with food was increased by 7 % and 19 %, respectively. The increase in Cmax as found not to be significant since the 90% geometric confidence interval fell within the 80.00-125.00% range. The 90% CI for AUCO-t and AUCO-inf however were found to fall slightly outside the 8 0. 00
- 125.00%. range (90% CI for AUCO-t =1 13.23 - 126.06%; 90% CI for AUCO-inf =112.96 - 125.52 %). This marginal failure of not being within the 80.00% - 125.00% was concluded

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not to be clinically significant. Lastly, the presence offood did not lead to a change in the
Tmax of bupropion.

Similar outcome were observed with hydroxybupropion, bupropion erythroamino alcohol and
5 bupropion threoamino alcohol.

For PAWC, food had no significant influence on the Cmax and AUCs with the 90% CI
failing within the 80.00-125.00% range %.

10 In conclusion it was surmised that Bupropion HBr XL 348 mg Tablets does not exhibit a

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significant food effect when given as a single oral dose.

Overall, Bupropion I-IBr XL 348, mg Tablets were well tolerated as a single-dose of 348 mg, administered under fed and fasted conditions, and no significant safety issues emerged.

This study was performed in compliance with GCP.

Table: Mean (–SD) Pharmacokinetic Parameters for Bupropion (n = 48)
Fed Fasting
Bupropion Bupropion
HBr XL HBr XL

348 mg Tablets 348 mg Tablets
(06C159P) (06C159P)
(n48) (n48)
AUCO-t 1814–543 1515–414

(ng hr/mL)
AUCO- 1876–551 1572–421

(ng hr/mL)
Cmaxng/mL) 136.8–43.1 125.9–34,5
Trnax (hr) 5.0 (2.0 10.0) 5.0 (3.0- 7.0)
t (hr) 23.2–6.5 21.3–6.7
MRT(hr) 22.4–5.9 21.2–5.6
Median (Range)

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Table: Summary Statistics for Bupropion (n = 48)

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Bupropion HBr XL 348 mg Tablets: Fed Versus
Fasting

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-t 119.47% 113.23 to 126.06 %
AUCO- 119.07% 112.96 to 125.52
Cmax 107.48% 98.20to117.64%

Table: Mean (–SD) Pharmacokinetic Parameters for Hydroxybupropion (n = 48)
Fed Fasting
Bupropion Bupropion
HBr XL HBr XL
348 mg Tablets 348 mg Tablets
(06C159P) (06C159P)
(n=48) (n=48)
AUCO-t (ug hr/tnt) 25506 –13953 24948 –13334
AUCO- (ug hr/mL) 25871 –14033 25285 –13347
Cmax (ng/mL) 525.1 – 239.3 507.4 – 221.1
Tmax (hr) 14.0 (7.0 - 36.0) 8.0 (5.0 24.0)
t (hr) 24.8 –4.8 24.3–4.9
MRT(hr) 42.7–7.6 41.1–7.4
Metabolite/ Parent 13.2–6,0 15.5–7.3
Ratio

Median (Range).

Table: Summary Statistics for Hydroxybupropion (n = 48)

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Bupropion HBr XL 348 mg Tablets: Fed Versus
Fasting

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-t 101,95 95.40 to 108.96
AUCO- 102.01% 95.50 to 108.95
=ax 102.52% 96.75 to 108.62

Table: Mean (–SD) Pharmacolcinetic Parameters for Bupropion Tbreoarnino Alcohol (n = 48)
Fed Fasting
Bupropion Bupropion

HBrXL HBrXL

348 mg Tablets 348 mg Tablets
(06C159P) (06C159P)
(n=48) (n=48)
AUCO-t(ng hr/mL) 10455+5635 9356–4971
AUCO- ng hr/rnL) 11149–6125 10081–5605
Cmax(ng/mL) 193.8–83.6 168.4–69.8
Tmax (hr) 11.0 (5.0 -36.0) 7.0 (5.0-24.0)
t (hr) 50.5 15.2 50.8 – 18.5
MRT(hr) 69.3–20.0 70.0–23.8
Metabolite/ Parent 5.9 –2.9 6.4 –3.2
Ratio

Median (Range)

Table: Summary Statistics for Bupropion Threoamino Alcohol (n = 48)

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upropion HBr XL 348 mg Tablets: Fed Versus
Fasting

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-t 112.86% 106.31 to 119.80%
AUCO- 112.34% 105.67 to 119.42 %
Cmax 115.97% 107.44 to 125.18 %

.

Table: Mean (–SD) Pharmacokinetic Parameters for Bupropion Erythroarnino Alcohol (n 48)

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Fed Fasting
Bupropion Bupropion
HBrXL HBrXL

348 mg Tablets 348 mg Tablets
(06C159P) (06C159P)
(n48) (n48)
AUCO-t(ng hr/mL) 1977–822 1763 –764
ATJCO- (rig hr!rnL) 2069–835 1860–780
Cmax (ng/rnL) 34.9 – 10.4 30.2 – 8.8
Tmax (hr) 14.0 (8.0 - 36.0) 14.0 (5.0 36.0)
t (hr) 31.8–7.3 31,1–7.8
MRT(hr) 53.3–11.4 51.6–11.3
Metabolite/ Parent 1.1–0.4 1.2–0.4
Ratio

Median (Range)

Table: Summary Statistics for.Bupropion Erythroamino Alcohol (u = 48)

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Bupropion HBr XL 348 mg Tablets: Fed Versus
Fasting

Ratio of Geometric
Means

90 Geometric Confidence.
Interval
AUCO-t 114.07% 106.29 to 122.40
AUCO- 113.00 105.83 to 120.66%
Cmax 115.84% 108.36 to 123.83 %

Table: Mean (–SD) Pharmacokinctic Parameters for PAWC (n = 48)
Fed Fasting
Bupropion Bupropion
Pharmacokinctic HBr XL HBr XL
Parameters 348 mg Tablets 348 mg Tablets
(06C159P) (06C159P)
(n48) (n=48)
AUCO-t (jiM hr)) 78.5 35.5 74.8 33.1
AUCO- (jiM hr)) 79.1 36.1 75.3 33,3
Cmax(j.tM) 1.8–0.6 1.8–0.6
Tniax (hr) 10.0 (2.0 24.0) 5.5 (4.0 24.0)
t (hr) 26.4 6,2 26.3 7.4
MRT (hr) 42.3 7.7 41.5 8.4
Median (Range)

Table: Summary Statistics for PAWC (n = 48)

Bupropion HBr XL 348 mg Tablets: Fed Versus
Fasting

Ratio of Geometric 90 Geometric Confidence
Means Interval
AUCO-t 104.94% 98,67 to 111.60

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AUCO- 104.81% 98.47to111.56% Cmax 98-89% 92.74 to 105.44

Two-Way Crossover Fasting Steady State Dosage Strength Proportionality Study of
Bupropion Hydrobromide XL Tablets (522 mg vs 3x174 mg) in Healthy Non-Smoking Adult
5 Volunteers. Study B06-802PK-10121 (AA40055)

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The rate and extent of absorption of a Bupropion HBr XL 522 mg Tablet was studied relative
to 3 x Bupropion HBr XL 174 mg Tablets under multiple-dose fasting conditions. The 522
mg tablet was equivalent to 174 mg tablets given as 3 x 174 mg.

Results are shown below and in Figures 50-54,

Methodology:
This was an open-label, randomized, 2-way crossover, 2-sequence, multiple-dose, dosage
15 strength proportionality study under fasting conditions.

Number ofsubjects (planned and analysed):
A total of 40 healthy adult non-smoking subjects (29 males and 11 females) were dosed, and
29 subjects (21 males and 8 females) completed the study. Pharmacokinetic parameters were
20 calculated for subjects who completed the study. Safety assessment was performed for all
subjects who received at least one dose.

Main Criteria for Inclusion and Exclusion:

Forty (40) healthy adult non-smoking (for at least 3 months) male or female volunteers at the
25 ages of from 18 to 55 years were to be selected for inclusion in the study.

Test and Reference Products, Dose, Mode ofAdministration, and Batch Number:
Bupropion HBr XL 522 mg tablets (test product), Manufactured by Biovail Corporation;
Lot No.: 06M1 19P; Bulk Lot No.: 06M303.

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Bupropion I-IBr XL 174 mg tablets (product for titration and reference product), Manufactured by Biovail Corporation; Lot No.: 06M062P; Bulk Lot No.: 06D 117,

Duration ofTreatment:

5 This study involved an up-titration period of 8 days prior to the treatment period. In the
mornings of Days ito 3, all subjects were administered a one tablet dose (1 x 174 mg; reference product) with 240 mL ofwater at room temperature, under fasting conditions. In
the mornings ofDays 4 to 8, all subjects were administered a 2 tablet dose (2 x 174 mg,-
reference product for a total dose of 348 mg) with 240 rnL ofwater at room temperature, g;reference
10 under fasting conditions.

For 14 consecutive days (Days 9 to 22), subjects received either one 522 mg bupropion hydrobromide tablet (test product) or three 174 m.g bupropion hydrobromide tablets
(reference product for a total dose of 522 mg). In the mornings of Days 23 to 36, subjects
15 received the alternate treatment. There was no washout between the treatments. Subjects were
dosed under fasting conditions.

Criteria for Evaluation:

Study endpoints were the 90% confidence intervals ofthe ratios of least-squares means
20 (LSM) for the pharmacokinetic parameters AUCO-, Cmax,ss and Cmin,ss ofthe test to

25

reference formulation under fasting conditions.

Safety assessment included laboratory evaluations, sedation tests, neurological tests, physical examinations, adverse events, ECG monitoring and vital signs assessments.

Pharniacokinetics:

Pharmacokinetic analysis was conducted using non-compartmental analysis. The following parameters: AUCO, Crnax,ss, Tmax,ss, Cpd, Cmin,ss, Cssav, % Fluctuation and % Swing were calculated for bupropion, hydroxybupropioll, bupropion threoamirto alcohol and
30 bupropion erythroamino alcohol.

All pharmacokinetic parameters were also calculated for the pharmacologic activity-weighted composite (PAWC).

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Bupropion HBr XL 174 mg tablets (product for titration and reference product), Manufactured by Biovail Corporation; Lot No.: 06M062P; Bulk Lot No.: 06D 117.

Duration ofTreatment:

5 This study involved an up-titration period of 8 days prior to the treatment period. In the
mornings of Days ito 3, all subjects were administered a one tablet dose (1 x 174 mg,-

reference product) with 240 rnL ofwatcr at room temperature, under fasting conditions. g;reference In the mornings ofDays 4 to 8, all subjects were administered a 2 tablet dose (2 x 174 mg;
reference product for a total dose of 348 mg) with 240 mL of water at room temperature,
10 under fasting conditions.

For 14 consecutive days (Days 9 to 22), subjects received either one 522 mg bupropion hydrobrom.ide tablet (test product) or three 174 mg bupropion hydrobromide tablets
(reference product for a total dose of 522 mg). In the mornings of Days 23 to 36, subjects
15 received the alternate treatment. There was no washout between the treatments. Subjects were
dosed under fasting conditions.

Criteria for Evaluation:

Study endpoints were the 90% confidence intervals ofthe ratios ofleast-squares means
20 (LSM) for the pharmacokinetic parameters AUCO-, Cmax,ss and Cmin,ss ofthe test to
reference formulation under fasting conditions.

Safety assessment included laboratory evaluations, sedation tests, neurological tests, physical Sexaminations, adverse events, ECG monitoring and vital signs assessments.
25
Pharmacokinetics:

Pharmacôkinetic analysis was conducted using non-compartmental analysis. The following parameters: AUCO, Cmax,ss, Tmaxss, Cpd, Cmin,ss, Cssav, % Fluctuation and % Swing
were calculated for bupropion, hydroxybupropion, bupropion threoamino alcohol and
30 bupropion erythroamino alcohol.

All. pharmacokinctic parameters were also calculated for the pharmacologic activity-weighted composite (PAWC).

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In addition, the metabolite/parent (M/P) ratios based on AUCO corrected for molecular weight were calculated for all metabolites,

Safety:
Safety data, including laboratory evaluations, physical examinations, adverse events, FCC monitoring and vital signs assessments were summarized by collection time and by treatment group, when appropriate. Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) were calculated for quantitative safety data as well as for the
10 difference from baseline, if applicable. Frequency counts were compiled for classification of
qualitative safety data. In addition, a shift table describing out of normal range shifts was provided for clinical laboratory results. A normal-abnormal shift table was also presented for physical examination and EEG results.

15 Adverse events were coded using the latest version of MedDRA dictionary and summarized
by treatment for the number ofsubjects reporting the adverse event and the number of
adverse events reported. A by-subject adverse event data listing including investigator term, coded term, treatment group, severity, and relationship to treatment were provided.
Concomitant medications were listed by subject and coded using the latest version ofthe
20 WHO drug dictionary. Medical history was listed by subject and coded using the latest
version ofMedDRA dictionary.

Statistical Methods:

Descriptive statistics were performed for plasma concentrations and for all pharmacoidnetic
25 parameters. Using GLM procedure in SASfi, an analysis of variance (ANOVA) was
performed on In-transformed pharmacokinetic parameters AUCO-, Crnax,ss and Cmin,ss.
The intra-subject coefficient ofvariation (CV) was calculated using the mean square error
(MSE) from the ANOVA. The ratios of LSM and the 90% confidence intervals were
calculated based on the difference in the LSM ofthe in-transformed AUCO-, Cmax,ss and
30 Cmin,ss between the test and the reference formulation. Steady state was assessed using pre-
dose concentrations on Days 19, 20, 21 and 22 as well as on Days 33, 34, 35 and 36 based on Helmert’s contrasts. Bioavailability was evaluated on the basis ofthe 90% confidence
intervals ofthe ratios ofLSM ofthe test to reference formulation for the parent drug,

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metabolites and PAWC. Confidence interval percentages were within the 80.0 125.0% acceptance criteria.

The parameter Tmax,ss was analyzed using the nonparametric methods of Koch and
5 Hauschke. The equality oftreatment effect in both sequences was evaluated using Wilcoxon rank-sum tests. The shift between the two treatments was estimated by the median unbiased Hodges-Lehmann estimate and its 90% confidence interval. The Hodges-Lehmann procedure extends the Wilcoxon rank-sum test to provide a median unbiased point estimate and a confidence interval for the magnitude ofthe shift between two populations.
10

Summary / Results:
 Bupropion
The pharmacokinetic parameters of bupropion in plasma following oral administrations of Bupropion HBr XL 522 mg tablets and Bupropion HBr XL 174 mg tablets (total dose of 522
15 mg) are listed below:

Parameter Bupropion HBr XL 1 x 522
mg tablet

Bupropion HBr XL 3 x 174
mg tablets
Geometric Mean (% CV)
AUCO (nghlmL)
Cmax,ss (ng/mL)
Cmin,ss (ug/mL)

1655 (32.4%) 1677 (33.0%)
165(37.2%) 159(32.0%)
28.8 (44.6%) 28.9 (41.4%)
Median Tmax (Mm Max)
Tmax,ss (h) 4.00 (2.00 7.00) 5.00 (3.00 6,06)
Arithmetic Mean (– SD)
AUCO (ngh!mL)
Cmaxss(ug/mL)
Cmin,ss(ng/mL)
Cssav(ng/mL)
Fluctuation (%)
Swing (%)

1730–494 1763–574
176–63.6 167+53.0
31.4–13.4 31.3–13.2
72.1+20.6 73.5–23.9
200–48.6 187–24.9
522–251 468+143

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At steady state, the mean rate and extent ofsystemic exposure of bupropion within the 24 hours dosing interval (Cmax,ss, ATJCO) were similar between Bupropion HBr XL 1 x 522 mg tablet and Bupropion HBr XL 3 x 174 mg tablets. The mean % fluctuation and the mean
% swing values were 7% and 12%, respectively greater for Bupropion HBr XL 1 x 522 mg
5 tablet compared to Bupropion HBr XL 3 x 174 mg tablets.

The median Tmax,ss value of bupropion was 4.0 hours and 5.0 hours for Bupropion HBr XL
1 x 522 mg and Bupropion HBr XL 3 x 174 mg tablets, respectively. The non-parametric
90% confidence interval for the median Tmax,ss of the test - reference difference
10 (formulation effect), was [-1.00; 0.50] for bupropion.

15

Results ofthe ANOVA for bupropion in plasma following oral administrations ofBupropion HBr XL 1 x 522 mg tablet and Bupropion HBr XL 3 x 174 mg tablets (total dose of 522 mg)
are presented as follows:

Ratios ofLSM (90% Confidence Intervals)
Parameter Biovail Bupropion, HBr XL 1 x 522 mg
tablet (A) vs. Biovail Bupropion HBr XL 3
x 174 mg tablets (B)
AUCO- 97.8 (91.4 104.5 %)
Cmax,ss 103.2% (96.0% 111.0 %)
Cmin,ss E99.0 (90.7 108.0 %)

The 90 % confidence intervals ofthe ratio of LSM derived from the analyses of the In-transformed pharmacokinetic parameters AUC0, Cmax,ss and Crnin,ss for bupropion in
20 plasma were within 80.0-125.0%

25

Helmert’s contrasts results demonstrated that the relative bioavailability for bupropion for both dosage strength tablets (1 x 522 mg and 3 x 174 mg) was assessed under steady state conditions on Days 22 and 36.

Bupropion Metabolites

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The pharmacokinetic parameters of bupropion metabolites in plasma following oral administrations ofBupropion HBr XL 1 x 522 mg tablet and Bupropion HBr XL 3 x 174 mg tablets (total dose of 522 mg) are listed below.

Parameter Hydroxybupropion Bupropion Threoamino Bupropion
Alcohol Erythroamino Alcohol
Bupropion Bupropion Bupropion Bupropion Bupropion Bupropion
HBr XL HBr XL HBr XL HBr XL HBr XL HBr XL

1 x 522mg 3 x 174mg 1 x 522mg 3 x 174m.g 1 x 522mg 3 x 174mg
Geometric
Mean

(% CV)
ALICO- 25158 25271 13802 13658 2857 2831 (nghimL) (53.4%) (48.5%) (40.2%) (40.7%) (38.0%) (36.5%) Cmax,ss 1338 1311 753 731 146 144
(ng/rnL) (48.5%) (42.9%) (38.3%) (39.6%) (358%) (36.9%)
Cmin,ss 880 943 450 466 101 105

(ng/mL) (57.7%) (54.5%) (48.7%) (40.8%) (48.2%) (36.7%)

Median
Tmax,
(MmMax)
Ttnax, ss (h) 5.04 7.00 6.00 7.00 6.00 8.00
(2.00 (3.00- (2-03- (3.00 (2.00 (3.0o-
8.00) 12.00) 10.00) 14.00) 10.00) 16.00)
Arithmetic
Mean (-I--SD)
AUCO- 27738– 27389– 14840– 14730– 3048– 3006–
(nghlmL) 10583 9385 5929 6138 1135 1075
Cmax,ss 1457– 1402– 805–309 785–311 155–55.4 154–54.9
(ng/mL) 530 446
Cmin,ss 986–415 1042– 496–220 504–218 111–46.5 112–40.8
(ig/mI) 410

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Cssav 1156– 1141– 618–247 614–256 127–47.3 125–44.8
(ngtmL) 441 391
Fluctuation 43.0 34.9 – 52.1 46.7 37.1 – 33.5

(%) 17,3 15.4 19.0 13.3 17.0 12.6
Swing 55.1 40.5 71.9 58.3 47.3 38.6

(%) 32.8 20.8 45.3 20.3 32.9 16.9
MIP ratio 15.7– 16.0– 8.65– 8.47– 1.81 1.77–
6.82 8.35 2.70 2.83 0.599 0.610

At steady state, the metabolic ratios based on the AUCO- of hydroxybupropion, bupropion threoamino alcohol and bupropion erythroamino alcohol over bupropion were 15.7, 8.65, and 1.81, respectively, for the Biovail Bupropion HBr XL 1 x 522 mg tablet. Metabolic ratios
were similar when compared to Biovail Bupropion BBr XL 3 x 174 mg tablets.

The mean % fluctuation and the mean % swing values of all bupropion metabolites were comparable following both dosage strength tablets (1 x 522 mg and 3 x 174 mg tablets).

10 The median Tmax,ss value of hydroxybupropion and bupropion eiythroamino alcohol was
observed 2 hours earlier for Bupropion HBr XL 1 x 522 mg taiblet than for Bupropion HBr
XL 3 x 174 mg tablets. The median Tmax,ss value of bupropion threoamino alcohol was observed 1 hour earlier for Bupropion HBr XL 1 x 522 mg tablet than for Bupropion HBr XL
3 x 174 mg tablets. The nonpararnetric 90% confidence intervals for the median Tmax,ss of
15 the test -reference difference (formulation effect), were [-2.00; 0.00] for hydroxybupropion,
[-2.00; -0.50] for bupropion threoarnino alcohol and [-2.00; 0.001 for bupropion erythroaniino

alcohol.

The pharmacokinetic results of bupropion metabolites in plasma following oral
20 administrations ofBupropion HBr XL 1 x 522 mg and Bupropion HBr XL 3 x 174 mg tablets
(total dose of 522 mg) are listed below.

Ratios ofLSM (90% Confidence Intervals)
Parameter Hydroxybupropion Bupropion Bupropion
Threoaniino Erythroamino

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Alcohol Alcohol

Biovail Bupropion Biovail Bupropion Biovail Bupropion-
upropionHBrXL
HBr XL1 x522mg HBr XL ix 522 mg HBr XL 1 x522mg
(A) vs. Biovail (A) vs. Biovail (A) vs. Biovail
Bupropion HBr XL Bupropion HBr XL Bupropion HBr XL
3 x 174 mg tablets 3 x 174 mg tablets 3 x 174 mg tablets
(B) (B) (B)

AUCO- 99.5% 100.9% 100.7%

(95.3 % 104.0 %) (94.1 108.1 %) (94.6% 107.2%)

Cmax,ss 102.2% 102.6% 101.0%
(98.0 106.6 %) (95.4 110.3%) (94.8 107.6%)

Cminss 93.7% 96.6% 96.4%

(87.7 100.2 %) (88.2 105.7 %) (88.2 105.4%)

The 90 % confidence intervals ofthe ratio of LSM derived from the analyses ofthe in-transformed pharmacokinetic parameters AUCO-, Cmax,ss and Cmin,ss for all bupropion
5 metabolites were within 80.0-125,0%.

Is PAWC (Pharmacological Activity Weighted Composite)
The pharmacokinetic parameters of PAWC following oral administrations ofBupropion HBr
XL 1 x 522 mg tablet and Bupropion HBr XL 3 x 174 mg tablets (total dose of 522 mg) are
10 listed below.

Parameter PAWC
Bupropion HBr XL 1 x 522
mg tablet

Bupropion HBr XL 3 x 174
mg tablets

Geometric Mean (% CV)

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AUCO (nmolhlmL)
Cmax,ss (nmo‰iiL)
Cmin,ss (nmoilmL)

82.2 (39.1%) 82.9 (3.2.4%)
4.64 (34.7%) 4.51 (27.0%)
2.73 (45.5%) 2.91 (39.3%)
Median Trnax (Min Max)
Tmax,ss (h) 5.00 (2.00 7.00) 5.00 (3.00 12.00)
Arithmetic Mean (– SD)
AUCO (nmol h!mL)
Cmax,ss (nmollmL)
Cmin,ss nmo1ImL)
Cssavnmol/rnL)
Fluctuation (%)
Swing (%)

87.4 27.8 86.5 23.6
4.88 1.45 4.65 1.12
2.96 1,09 3.09 1.03
3.64– 1.16 3.61–0.983
55.2-+18.6 46.3 16.9
73.8–38.4 57.0–26.2

The nonparametric 90% confidence intervals for the median Tmax,ss ofthe test-reference difference (formulation effect) was [-1.50; -0.501 for PAWC.

5 The pharinacokinetic results for the PAWC dataset following oral administration of Bupropion HBr XL 1 x 522 mg tablet and Bupropion HBr XL 3 x 174 mg tablets (total dose of 522 mg) are listed below.
Ratios ofLSM (90% Confidence Intervals)
Parameter PAWC

Biovail Bupropion HBr XL 1 x 522 mg tablet (A) vs.
Biovail BupropionHBr XL 3 x 174 mg tablets (B)
AUCO- 99.1 (94.6 103.8 %)
Cmax,ss 102.9 (98.2 107.7%)
Cmin,ss 94.2%(87.9%-100.9%)

10 The 90,% confidence intervals ofthe ratio of LSM derived from the analyses ofthe hi-transformed pharmacokinetic parameters AUCO-, Cmax,ss and Cmin,ss for PAWC were within 80.0-125,0%.

Conclusion:

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Following repeated oral administrations of bupropion Hydrobromide XL Tablets (522 mg vs.
3 x 174 mg) in healthy volunteers, the 90 % confidence intervals ofthe ratios ofLSM derived from the analyses ofthe in-transformed pharmacokinetic parameters AUCO-, Cmax,ss and Cmin,ss for bupropion, hydroxybupropion., bupropion threoamino alcohol, bupropion erythroamino alcohol and PAWC in plasma were within 80.0-125.0%.

In conclusion, results from the current dosage strength proportionality study demonstrated that repeated oral administrations ofBiovail bupropion hydrobromide XL tablets as a single 522 mg tablet and three 174 mg tablets are equivalent under multiple dose fasting conditions.

Table Mean (–SD) Pharrnacokinetic Parameters for Bupropion (n = 29)
1 x Bupropion HBr 3 x Bupropion HBr
XL XL

522 mg Tablet 174 mg Tablets
(06M1 19P) (06M062P)
(n’29) (n=29)
AUC0- (ug hr/mL) 1730–494 1763574
Cmax(ng/mL) 176.1–63.6 166.9–53.0
Cmin(ng/mL) 31.4–13.4 31.3–13.2
Cavg(ng/rriL) 72.1–20.6 73.5–23.9
Tmax(hr) 4.0(2.0,7.0) 5.0(3.0,6,1)
Degree of
199.9–48.6 186.7–24.9

Fluctuation (%)
Median (Range)

Table Summary Statistics for Bupropion (n = 29)

1 x Bupropion HBr XL 522 mg Tablet
Versus 3 x Bupropion HBr XL 174 mg Tablets

Ratio ofGeometric 90 Geometric Confidence Means Interval

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AUCO-T 97.8% 91.4 -104.5
Cmax 103,2% 96.0-111.0%
Crnin 99.0% 90.7 108.0

Table: Mean (–SD) Pharmacokinetic Parameters for Hydroxybupropion (n = 29)
1 x Bupropion HBr 3 x Bupropion HBr
XL XL

522 mg Tablet 174 mg Tablets
(06M1 19P) (06M062P)
(n29) (n=29)
AUC0-(ng hr/mL) 27738–10583 27389–9385
Cmax (ng/mL) 1457.0–530.3 1401.9–445.8
Cmin (ng/mL) 985.9–414.8 1042.4–410.4
Cavg (ng!mL) 1155.7–441.0 1141.2–391.0
Tmax (hr) 5.0 (2.0, 8.0) 7.0 (3.0, 12.0)
Degree ofFluctuation
43.0–17.3 34.9–15.4
(%)
Metabolite/ Parent
15.7–6.8 16.0–8.3
Ratio

Median (Range)

Table: Summary Statistics for Hydroxybupropion (n = 29)

1 x Bupropion HBr XL 522 mg Tablet
Versus 3 x Bupropion HBr XL 174 mg Tablets

Ratio ofGeometric
Means

90 Geometric Confidence
Interval
AUCO-t 99.5% 95.3 104.0
Cmax 102.2% 98.0 106.6
Cniin 93.7% 87.7 100.2

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Table Mean (–SD) Pharmacokinetic Parameters for Bupropion Threoamino Alcohol (n = 29)
1 x Bupropion HBr 3 x Bupropion HBr
XL XL

522 mg Tablet 174 mg Tablets
(06M1 19P) (06M062P)
(n29) (n29)
AUC0-(ng hr!mL) 14840–5929 14730–6138
Cmax (ng/mI..) 805.2–3008,7 784.9–310.9
Cmin(ng/mL) 496.2–219.5 503.6–217.9
Cavg (ng/mL) 618.4–247.1 613.8–255.8
Tmax (hr) 6.0 (2.0, 10.0) 7.0 (3.0, 14.0)
Degree of Fluctuation
51.2–19.0 46.7–13.3

(%)
Metabolite/ Parent
8.7–2.7 8.5–2.8
Ratio

Median (Range)

5 Table: Summary Statistics for Bupropion Threoamino Alcohol (n = 29)

1 x Bupropion HBr XL 522 mg Tablet
Versus 3 x Bupropion HBr XL 174 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUC0- 100.9 94.2 108.1
Cniax 102.6% 95.4-110.3%

rcM

 in 96.6 88.2 105.7
Table Mean (–SD) Pharmacokinetic Parameters for Bupropion Erythroamino Alcohol (n = 29)
1 x Bupropion HBr 3 x Bupropion HBr
XL XL

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522 mg Tablet 174 mg Tablets
(06M1 19P) (06M062P)
(n=29) (n29)
AUC0T(ng hrlmL) 3048–1135 3006–1074
Cmax(ng/mL) 155.3–55.4 153.6–54,9
Cmin(ng!mL) 111.3–46.5 111.6–40.8
Cavg(ng/mL) 127.0–47.3 125.3–44.8
Tmax (hr) 6.0 (2.0, 10.0) 8.0 (3.0, 16.0)
Degree of luctuafion
37.1+17.0 33.5–12.6
(%)
Metabolite/Parent
1.8–0.6 1.8–0.6
Ratio

Median (Range)

Table: Summary Statistics for Bupropion Erythroamino Alcohol (n 29)

1 x Bupropion HBr XL 522 mg Tablet
Versus 3 x Bupropion HBr XL 174 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-c 100.7% 94.6 107.2
Cmax 101.0% 94.8 107.6
Crnin 96.4% 88.2-105.4%

Table: Mean (–SD) Pharmacokinetic Parameters for PAWC (n = 29)
1 x Bupropion HBr 3 x Bupropion HBr
XL XL
Pharmacokjnetjc
522 mg Tablet 174 rng Tablets
Parameters

(06M1 19P) (06M062P)
(n=29) (n=29)
87.4–27.8 [86.5–23.6

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(nmol hr/mL)
Cmax(nmoLlrnL) 4,9+1.5 4.7–1.1
Crnin(nmol/mL) 3.0–1.1 3.1–1.0
Cavg(nmol/mL) 3.6–1.2 3.6–1.0
Tmax (hr) 5.0 (2.0, 7.0) 5.0 (3.0, 12.0)
Degree of
Fluctuation (%)

55.2–18.6 46.3–16.9

Median (Range)

Table: Summary Statistics for PAWC (ii = 29)

1 x Bupropion HBr XL 522 mg Tablet
Versus 3 x Bupropion HBr XL 174 mg Tablets

Ratio of Geometric
Means

90 Geometric Confidence
Interval
AUCO-’t 99.1 94.6 103.8
Cmax 102.9% 98.2-107.7%
Cmiii 194.2% 87.9 100.9

EXAMPLE 8

The analysis of 3 ’-Chloro-2-bromopropiophenone impurity in Bupropion HBr samples in this example is based on a HPLC LIMIT TEST. The impurity peak, eventually present in the
sample chromatogram, should not exceed in area the peak ofthe ana!yte in the "reference
10 solution" chromatogram corresponding to a concentration of 3 ppm ofimpurity in the sample. The method uses a C18 column with UV detection at 255 n:m and an isocratic mobile phase.

Operating conditions
Instrument: Shimadzu HPLC pump LC- 1OAD, system controller SCL- 1 OA, autoiuj ector S1L- 1 OA
(Or equivalent)

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Column: phase: Waters XBridge C18
particle size: 5 mm
column length: 250 mm
column ID: 4.6 min
Injection volume: 50 ml
Detector: Shirnadzu UV detector model SPD-JOA (or
equivalent)
Wavelength: UV, 255 urn
Mobile phase: see preparation below
Column T: 40°C
Flow: 1.2m1/min.

Mobile phase: mix 1100 ml of acetonitrile and 1000 ml of Na2HPO4 20 mM solution in
HPLC water. Adjust the pH to pH 7.2 with phosphoric acid 85%.

5 Sample solution: weigh accurately 500 mg ofsample and transfer into a 50 ml volumetric
flask. Dissolve and dilute to volume with HPLC water (10 rng/rnl).

Reference solution (3 ’-Chloro-2-bromopropiophenone 3 ppm spiked solution): weigh accurately 15 mg – 1 mg) of 3’-Chloro-2-bromopropiophenone WSTD into a 100 ml
10 volumetric flask. Dissolve and dilute to volume with acetonitrile (0.15 rngirnl, sol.A). Pipet
accurately 1.0 ml of "sol.A" into another 100 ml volumetric flask and dilute to volume with HPLC water (0.0015 mg/ml, sol, B). Into a 50 ml volumetric flask weigh about 500 rng of Bupropion.HBr WSTD and add accurately 1.0 ml of "sol.B". Dissolve and dilute to volume
with HPLC water (Bupropion.HBr 10 mg/ml and analyte 0.03 gg/ml, which corresponds to
15 0.0003% (3ppm) ofthe sample concentration 10,000 gg/ml).

System suitability test: condition the HPLC system with the prescribed ’operating conditions" until a stable, fiat baseline is obtained then inject 50 ml of ’reference solution". Allow the
analysis to carry on. The system suitability test is complied if:
20 1) Specificity and sensitivity: The peak of 3’-Chloro-2-bromopropiophenone is resolved from the Bupropion and other eventual impurity peaks and has an RT of 13
– 2 The peak area ofthe analyte is NLT 5000.

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2) Precision: the RSD% of all analyte peak areas obtained in the "reference solution" chromatograms is NMT 20%.

Procedure: on system suitability compliance separately inject 50.d ofreference and sample solutions. Record the chromatograms and measure the peak area responses ofthe 3’-Chloro-2-bromopropiophenone impurity peaks.

Evaluation:
Identification: identify the 3’-Chloro-2-bromopropiophenone impurity in the sample runs, if
10 present, by comparing the peak RTs with the "reference solution" runs. The expected RT is tabulated below:
RT/ RRT TABULATION

Compound RTmin,
3’-chloro-2-bromopropiophenone 13 min. 2

Limit evaluation: any peak, eventually present on the sample chromatogram identified as 3’- Chloro-2-bromopropiophenone should have a peak area NMT the mean peak area ofthe 3’-
15 Chloro-2-bromopropiophenone in the "reference solution" replicates corresponding to a

20

content of 3 ppm (0.0003%) impurity in the sample. For the result report consider the
following tabulation:
RESULT REPORTING TABULATION

Impurity Report
the 3’-chloro-2-bromopropiophenone peak
area is lower than the 3 ppm reference area

3 ppm

the 3 -ehloro-2-bromopropiopheuone peak
area is higher than the 3 ppm reference area

3 ppm

METHOD SENSITIVITY
Impurity LOQ LOD 3’-chloro-2-
bromopropiophenone

not applicable to limit test 1 ppm
(0.01.tg/m1
1 ppm or 0.0001% in regards to the sample concentration 10,000).ig!ml.

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Results:

This example describes a I-JPLC/IJV method specifically for detecting the 3 ’-chloro-2-bromopropiophenone impurity. To increase sensitivity the UV wavelength ofthe detector was set at the maximum absorbance for the analyte corresponding to 255 rim and the mobile 5 phase was adjusted to sharpen the analyte peak as much as possible. The method operating

10

conditions as a "3 ppm LIMIT TEST" are reported herein. The tabulated batches of API were tested. Results show that 3 ’-Chloro-2-bromo-propiophenone is well below the practical
detection limit of 1 ppm in each batch tested.

BATCH ANALYSIS RESULTS
3 PPM LIMIT TEST FOR 3’-CHLORO-2-BROMO-PROPIOPHENONE
IN BUPROPION HYDROBROMIDE
BATCH RESULT
D00894 NOT DETECTABLE
D00895 NOT DETECTABLE
D00896 NOT DETECTABLE
06PK0970 NOT DETECTABLE
06PK0971 NOT DETECTABLE

LIMIT OF DETECTION: 1 ppm

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Table 1: Each trial’s contents and amounts of each material per part
Materials Amount (g)
Part 1 Part Part Part part
Bupropion T-TBr 2062.5 2062.5 2062.5 2062.5 2062.5
PVA 68.75 68,75 68.75 68.75 68.75
Purified Water 1452.5 1452.5 1452.5 1452.5 1452.5

5 Table 2: Summary ofspecifications for granulation procedure.
Specification Range Target
Fan Speed Slow. Slow
Air Volume (CMH) 60-65 65
Exhaust Temperature (°C) 35-45 40
Supply Temperature (°C) 60-65 65
Product Temperature (°C) 35-55 45
Atomizing Air Pressure (Bar/psi) 35 35
Pump Speed (rpm) 18 18
Liquid Flow Rate (g/min) 13 13
Bed Dew Point (MMWC) 0 0
Filter Dew Point (MMWC 100-300 200

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Table 3: The amount of lubricant in the final formulation was 343.75g, which was 3.125% of the total.

Materials Amount (g)
Part 1 2131.25
Part 2131,25
Part 3 2131.25
Part 4 2131.25
Part 5 2131.25
COMPJTOLfi
Total 11000.0

Table 4: Summary of Specifications for Tablet Press Set-up.

Parameters

Pre-Compression Thickness (mm) 2
Control Thickness (mm) 1.5
Fill Thickness (mm) 7-8
Overload Pressure (Tons) 1.5-2.0
Tablets per minute 450-500
Feeder Speed 1-2
Feeder Control Auto

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Table 5: Summary of specifications for compression

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Parameters Specification for Specification for
174mg Tablet 348mg Tablet
Individual Tablet Weight (mg) 185.6 5% 371,2 5%
(176.3mg-194.9mg) (352.6mg-389.8mg)
Average Tablet Weight (mg) 185.6 3% 371.2 3%
(180.0mg19 1.2mg) (360. lmg-382.3mg)
Tablet Hardness (SC) 6.0-12.0 6.0-12.0
Tablet Thickness (mm) 5.0-6.0 4.5-5,0
Friability (%) 0.8 0.8

Table 6: Formulations used as the ethylcellulose (e.g. ETHOCELfi or EC) coating on the
5 174mg and 348mg Bupropion HBr cores.
FORMULATION 1 FORMULATION 2 FORMULATION 3

ETHOCELfi (Ethyl ETHOCELfi (Ethyl ETHOCELfi (Ethyl
Cellulose) Cellulose) Cellulose)
Standard 100 Premium Standard 100 Premium Standard 100 Premium
Povidone USP Povidone USP Povidone USP
(KOLLIDONfi 90F) (KOLLIDONfi 90F) (KOLLIDON(D 90F)
Polyethylene Glycol 4000 Polyethylene Glycol 4000 Polyethylene Glycol 4000
Ethyl Alcohol 95% USP Dibutyl Sebacate Ethyl Alcohol 95% USP
Isopropyl Alcohol (IPA) Ethyl Alcohol 95% USP

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Table 7: Formulations used as the Final Coats on the 174mg and 348mg Bupropion HBr tablets.
FORMULATION A FORMULATION B
EUDRAGITfi L30D-55 EUDRAGITfi L30D55
Chrorna-Tone DEB 5156-CLE SYLOIDfi 244FP

Purified Water Polyethylene Glycol 4000
Triethyl Citrate
Purified Water

5 Table 8: Summary of Specifications that were kept constant
in the ethylcellulose coating Process.
Process Parameters Operational Target
Ranges
Inlet Temperature for coating (°C) SV:40 5 40
PV: 40–5

Inlet Temperature for Drying (°C) 30-35 35
Exhaust Temperature 30 10 30
Product Temperature 25-35 28
P Differential Pressure (W.C) (-0.1)-(-0.12) -0.10
Supply Air Flow (CFM) 200–50 200
Pan Speed (rpm) 2.5-12 5.0
Atomizing Air (psi) 35-40 35
Pattern Air (psi) 20-30 25
Spray Rate (g/min) 5-15 6.0

Table 9: Summary of Specifications that were kept constant in the Final coating Process.
Process Parameters Operational Target
Ranges
Inlet Temperature for coating (°C)SV:50–550

PV: 50–5

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Inlet Temperature for Drying (°C) 40 – 5 40
Exhaust Temperature 35 – 5 38
Product Temperature
P Differential Pressure (W.C)
Supply Air Flow (CFM)

35–2 35
-0.10
200–50 200

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Pan Speed (rpm) 2.5-15 12.0
Atomizing Air (psi) 25-35 35
Pattern Air (psi) 20-30 25
Spray Rate (g/min) 5-15 13.0

Table 10: Materials used in one part ofthe batch, the percentage of each constituent, the amount per tablet and the amount per batch, for BUPHBr-XL-009-5
Materials mg/tablet Batch Quantity (g)
BupropionHBr 93.75 348.00 1993.75
PVA 3.125 11.60 68.75
COMPRITOLfi 888 3.125 11.60 68.75
Total 100.00 371.2mg 2131.25
5

Table 11: Results obtained using 9mm tooling for batch BUP-HBr-XL-009-5.
Parameters Theoretical Actual

 AverageIndividual Tablet Weight-2mg 371 371.5mg
Average Hardness 6.0-12.0 SC 10.77 SC
Average Thickness 5.0-6,0mm 5.60 mm
Friability 0.8% 0%

10 Table 12: Results obtained using 10mm tooling for batch BUP-HBr-XL-009-5.

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meters Theoretical Actual
Average Individual Tablet Weight 371.2mg 366.5mg
Average Hardness 6.0-12,0 SC 7.50 SC
Average Thickness 5.0-6.0mm 4.97 mm
5 Friability 0.8% 0%

Table 13: Materials used in one part ofthe batch, the percentage of each constituent, the amount per tablet and the amount per batch for batch BUP-HBr-XL-021-5.
Materials % mg/tablet Batch Quantity (g)
BupropidnHBr 93.75 174.00 1993.75
PVA 3.125 5.80 68.75
COMPRITOLfi 888 3.125 5.80 68.75
Total 100,00 185.60 2131.25
10

Table 14: Results obtained using 7mm tooling for batch BUP-HBr-XL-021-5.
ameters Theoretical Actual

Average Individual Tablet Weight 185.6mg 186.8mg
Average Hardness 6.0-12.0 SC 9.23SC
Average Thickness 4.5-5.0mm 4.70mm
Friability 0.8% 0%

Table 15: Materials used in the ethylcellulose coating and their quantities for batch BtJP-

15 HBr-XL-348-013-5.
Materials % Batch % of Solids
Contribution Quantity in Solution
to Total (g)
Solution

ETHOCELfi (Ethyl Cellulose) Standard 100 3.60 77.44 38.74
Premium

Povidone LISP (KOLLIDONfi 90F) 4.600 99.22 49.64

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PEG 4000 1,07 23.23 11.62
Ethyl Alcohol 95% USP 86.44 1859.50 N/A
Isopropyl Alcohol 99% USP 4.54 97.87 N/A
Total 100.00 2151.00 100.00

Total solid component ofthe formulation included 77.44g of ethylcellulose (e.g. ETHOCELfi), 99.22g ofPovidone and 23.23g ofPEG 4000, which gave a total solid amount of 199.89g. The solid component ofthe formulation made up 9% ofthe total solution and the remaining 91% was made up ofliquid.

Table 16: Theoretical and Actual Tablet weights at 28mg, 30mg, 32mg and 34 mg weight gains for batch BUP-HBr-XL-348-013-5.

Weight Weight Actual Weight 3
28.0 400.0 401.3
30.0 402.0 402.6
32.0 404.0 404.5
34.0 406.0 406.8

10 Table 17: Materials used in the Final coating and their quantities for batch BUPHBr-XL-348-013-5.
Materials Batch Amount of
Contribution Quantity of Solid Solids
to Total (g) (g) in
Solu’iion Solution
ETJDRAGITfiL3OD-55 22.73 104.8 31.44 65.00
Chroma-Tone DEB 5156-CLE 3.66 16.90 16.90 35.00
Purified Water (1) 21.78 100.40 N/A N/A
Purified Water (2) 51.89 239.20 N/A N/A
Total 100.00 460.95 48.34 100.00
The percentage ofEUDRAGITfi, solid, that contributed to the total amount ofsolid was
65%.

The percentage of Chroma-Tone, solid, that contributed to the total amount of
15 solid was 35%.

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The Total amount ofsolid (4834g) was 10.5% ofthe total solution.

Table 18: Theoretical and Actual Tablet weights at 4mg, 5mg, 6mg and 7mg weight gains.
Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg)
4.0 410.0 410.5
5.0 411.0 410.8
6.0 412.0 412,4
7.0 413.0 413.9

5

Table 19: Materials used in the ethylcellulose coating and their quantities for hatch BUP-HBr-XL-348mg-018-5.
Materials Batch of
Contribution Quantity Solids in
to Total (g) Solution
Solution

ETHOCELfi (ethylceihilose) Standard 100 3.42 73.57 38.00
Premium

Povidone USP (KOLLIDONfi 90F) 4.41 94.86 49.00
PEG 4000 1.17 25.17 13.00
Ethyl Alcohol 9S%USP 86.45 1859.53 N/A
Isopropyl Alcohol 99% USP 4.55 97.87 N/A
Total 100.00 2151.00 100.00
Total solid included 73.57g of ethylcellulose 94.86g of PovidOne and 25.17g of PEG 4000.
This gave a total of 193.6g total solid amount.
10

Table 20: Theoretical and Actual Tablet weights at 26mg, 2 8mg, 3 0mg, and 32mg weight
gains for batch BUP-HBr-XL-348mg-01 8-5.
Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg)
26.0 398.0 397.7
28.0 IMC 399.5
30.0 402.0 401.5

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32.0 404.0 404.0

Table 21: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-348mg-0 18-5.
Materials

to Total Quantity Solid in Solution
Solution (g) (g)
EUDRAGITfiL3ODD-55 22.75 104.86 31.46 65.00
SYLOITJfi244FP 2.62 12.08 12.08 25.00
CARBOWAXfi 4000 0.70 3.22 3.22 6.65
Triethyl Citrate 0.36 1.64 1.64 3.39
Purified Water (1) 33.84 156.00 N/A N/A
Purified Water (2) 39.73 183.15 N/A N/A
Total 100.00 460.95 48.40 100,00
5 The percentage of EUDRAGITfi, solid, that contributed to the total amount ofsolid was 65%.

The percentage of SYLOIDfi, CARBOWAXfi 4000 and Triethyl Citrate that contributed
to the total amount ofsolid was 25%, 6.65% and 3.39%, respectively. This gave a total of 35%,
10 The total amount ofsolid (48.4g) was 10.5% ofthe total solution.

Table 22: Theoretical and Actual Tablet weights at 4mg, 5mg, 6mg, and 7mg weight gains
for batch BUP-HBr-XL-348mg-018-5.
Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg
4.0 408.0 408.5
5.0 409.0 409.3
6.0 410.0 410.7
7.0 411.0 411.1

15

Table 23: Materials used in theethylcellulose coating and their quantities for batch BliP-HBr-XL- 1 74mg-022-5.

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Materials Batch of Solids
Contribution Quantity in
to Total (g) Solution
Solution

ETHOCELfi (ethylceliulose) Standard 100 3.60 116.12 40.00

Premium

Povidone USP (KOLLIDONfi 90F) 4.32 139.34 48.00
PEG 4000 1,08 34.84 12.00
Ethyl Alcohol 95% USP 86.45 2788.54 N/A
Isopropyl Alcohol 99% IJSP 4.55 146.76 N/A
Total 10000 3225.60 100.00
Total Solid included 116.12g ofETHOCELV, 139.34g of Povidone and 34,84g ofPEG
4000. This gave a total solid amount of 290.3g.

Table 24: Theoretical and Actual Tablet weights at 20mg, 22mg, 24mg, 26mg, 28mg, 29mg,
5 and 30mg weight gains for batch BUP-HBr-XL174mg-022.-5.
Weight Gain mg Theoretical Weight (mg) Actual Weight mg
20.0 206.0 206.1
22.0 208.0 207.8
24.0 210.0 210.2
26.0 212.0 211,5
28.0 214.0 213.7
29.0 215.0 214.9
30.0 216.0 216.5

Table 25: Materials used in the Final coating and their quantities for batch BIJP-HBr-XL-1 74mg-022-5,
Materials % Batch Amount of % of Solids
Contribution Quantity Solid in Solution
to Total (g) (g)

Solution

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EUDRAGITfiL3ODD-55 22,75 104.86 31.46 65.0
SYLOIDfi 244FP 2.62 12.08 12.08 25.0
CARBOWAXfi 4000 0.70 3.22 3.22 6.65
Triethyl Citrate 0.36 1.64 1.64 3.39
Purified Water (1) 33.84 156.00 N/A N/A
Purified Water (2) 39.73 183.15 N/A N/A
Total 100.00 460.95 48.40 100.00

The percentage of EUDRAGITfi, solid, that contributed to the total amount ofsolid was
65%.

The percentage of SYLOIDfi, CARBOWA.Xfi 4000 and Triethyl Citrate that contributed
to the total amount of solid was 25%, 6.65% and 3.39%, respectively. This gave a total of
5 35%.
The Total amount ofsolid (48.4g) was 10.5% of the total solution.

Table 26: Theoretical and Actual Tablet weights at 4mg, 5mg, 61ng, and 7mg weight gains
fr batch BUPHBr-XL- 1 74mg-022-5.
Weight Gain (mg) Theoretical Weight ’mg Actual Weight rng)
4.0 219.0 219.4
5.0 220.0 220.2
6.0 221.0 221.2
7.0 222.0 223.0
10

Table 27: Materials used in the ethylcellulose coating and their quantities ’for batch BTJP-HBr-XL348mg-023-5.
Materials Batch of
Contribution Quantity Solids in
to Total (g) Solution
Solution

Premium

Povidone USP (KOLLIDONfi 90F) 3.69 79.37 42.71
PEG 4000 1.26 27.11 14.58

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1Sebacate,NF05N/A
Ethyl Alcohol 9S%USP 91.00 1957,4 N/A
Total 100.00 2151.00 100.00
Total Solid includes 79.37gofETHOCELfi,79.37gofPovidoie,27.11gof PEG 4000 and 7.75g of Dibutyl Sebacate. This gave a total solid amount of 193.6g.

Table 28: Theoretical and Actual Tablet weights at 26mg, 28mg, 30mg, and 32mg weight
5 gains for batch BUP-HBr-XL-348mg-023-5.
Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg)
26.0 398.0 399.3
. 28.0 400.0 401.0
30.0 402.0 401.7
32.0 404.0 402.7

Table 29: Materials used in the ethylcellulose coating and their quantities for batch BlIP-HBrXL-348mg025-5.
Materials Batch of
Contribution Quantity Solids in
to Total (g) Solution
Solution

ETHOCELfi (ethylcellulose) Standard 100 3.69 79.40 41.00
Premium

Povidonc lISP (KOLLIDONfi 90F) 3.78 81.30 42.00
PEG 4000 1.53 32.90 17.00
Ethyl Alcohol 95% USP 91.00 1957.40 N/A
Total 100.00 2151.00 100.00
10 Total Solid included 79.40g ofETHOCELfi, 81..30g of Povidone and 32.90g of PEG 4000. This gave a total solid amount of 193.6g.

Table 30: Theoretical and Actual Tablet weights at 261ng, 28mg, 30mg, and 321ng weight
gains for batch BUP-HBr-XL-348mg-025-5.

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Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg)
26.0 398.0 397.8
28.0 400.0 400.6
30.0 402.0 401.4
32,0 404.0 402.2

Table 31: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-348mg-025 -5.
Materials Batch Amount of of
Contribution Quantity (g) Solid Solids in
to Total (g) Solution
Solution
ETJDRAGITfiL3ODD-55 19.77 91.13 27.34 56.50
SYLOIDfi244FP 3.15 14.52 14.52 30.00
CARBOWAXfi 4000 0.95 4.36 4.36 9.00
Triethyl Citrate 0.47 2.17 2.17 4.50
Purified Water (1) 21.70 100.00 N/A N/A
Purified Water (2) 53.96 248.77 N/A N/A
Total 100.00 460.95 48.39 100.00
5 The percentage of EUDRAGITfi, solid, that contributed to the total amount ofsolid was 65%.

The percentage of SYLOIDfi, CARBOWAXfi 4000 and Triethyl Citrate that contributed
to the total amount of solid was 30%, 9% and 4.5%, respectively. This gave a total of 43.5%. The Total amount ofsolid (48.39g) was 10.5% ofthe total solution.
10

Table 32: Theoretical and Actual Tablet weights at 4mg, 5mg, 6mg, and 7mg weight gains
for batch BUP-HBr-XL-348mg-025-5.
Weight Gain (mg) Theoretical Weight mg Actual Weight (mg)
4.0 408.0 408.3
5.0 409.0 408.8
6.0 410.0 409.5

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7.0 41 LO 411.1

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Table 33: Materials used in the ethylcellulose coating and their quantities for batch BIJP-HBr-XL-348mg-026-5.
Materials Batch % of
Contribution Quantity Solids
to Total (g) Solution
Solution
ETHOCELfi (ethylcellulose) Standard 100 3.69 79,37 41.00
Premium

Povidonc USP KOLLIDONfi 90F) 3.69 79.37 41.00
PEG 4000 0.36 7.75 4.00

DibutyiScbacate,NF 1.26 27.11 14.00
Ethyl Alcohol 95% USP 91.00 1957.4 N/A
Total 100.00 2151.00 100.00

5 Total Solid included 79.37g ofETFIOCELfi, 79.37g of Povidone, 7.75g of PEG 4000 and 27.11g ofDibutyl Sebacate. This gave a total solid amount of 193.6g.

Table 34: Theoretical and Actual Tablet weights at 26mg, 28mg, 30mg, and 32mg weight gains for batch BUPHBr-XL-348mg-026-5.
Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg)

26.0 398.0 398.8
28.0 400.0 400.5
30.0 402.0 402.5
32.0 404.0 403.6
10

Table 35: Materials used in the ethylcellulose coating and their quantities for batch BliP-HBr-XL- 1 74m.g027-5.
Materials Batch % of
Contribution Quantity Solid in

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to Total (g) Solution
Solution

ETHOCELfi (ethylcellulose) Standard 100 3.69 138.87 41.00
Premium

Povidone USP (KOLLIDONfi 90F) 3.78 142.25 42.00
PEG 4000 1.53 57.58 17.00

Ethyl Alcohol 95% USP 91.00 3424.63 N/A
Total 100.00 3763.33 100.00

Total Solid included 138.87g ofETHOCELfi, 142.25g of Povidone and 57.58g ofPEG
4000. This gave a total solid amount of 338,7g.

Table 36: Theoretical and Actual Tablet weights at 22mg, 24mg, and 26mg weight gains for
5 batch BUP-HBr-XL-174mg-027-5.
Weight Gain (mg) Theoretical Weight (mg) Actual Weight (mg)
22.0 208.0 207.7
24.0 210.0 210.8
26.0 212.0 212.4

Table 37: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-
1 74mg-027-5.
Materials Batch Amount of
Contribution Quantity of Solid Solids in
to Total (g) (g) Solution
Solution
EUDRAGITfi L30D D-55 19.77 182.27 54.68 56.5
SYLOIDfi 244FP 3.15 29.03 29.03 30.0
CARBOWAXfi 4000 0.95 8.71 8.71 9.0
Triethyl Citrate 0.47 4.35 4.35 4.5
Purified Water (1) 21.70 200.00 N/A N/A
Purified Water (2) 53.98 497.26 N/A N/A
Total 100.00 921.62 96.77 100.00

The percentage of EUDRAGITfi, solid, that contributed to the total amount ofsolid was
10 56.5%.

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The percentage of SYLOIDfi, CARBOWAXfi 4000 and Thethyl Citrate that contributed
to the total amount ofsolid was 30.0%, 9.0% and 4.5% respectively.
This gave’. a total of 43.5%.
The Total amount ofsolid (9.77g) was 10.5% ofthe total solution.

Table 38: Theoretical and Actual Tablet weights at 4mg, 5mg, 61ng, and 7mg weight gains for batch BUP-HBr-XL- 1 74mg-027-5.
Weight Gain (mg) Theoretical Weight mg Actual Weight (mg)
4.0 216.0 216.6
5.0 217.0 217.6
6.0 218.0 217.8
7.0 219.0 219.8

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- - - - - - - - - t-----f----- T-1 to TO 1
I

RFiO> -.

HOFOC(OFF T-1 TO
QOA4 4.

J4L. to

itar I j
- ’ r ,....-

T*TO O1 I I

cci
NM F1s.

J4J 4 wkrj00
1.1 to TO: basdi’le felldl 1Nwp feiftoc).
TOO T2

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Table 40(1)

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*24 I

44(4,,4, i

I 4!

 . -. ..,. ----------------------- 44$’

42Jfl4...........

- - - - - - - - - - - - - - - 4.-------------------------4---
I 44, (’,4 (4 ( ’44’!,

. !:------------------------ ---------

’’’’’’’’’,"--’--"--- --r --...........,’ 7., -’lids ION.4-.il14
 , ...’ 20 4 ’(-4 4(4(4-, 44 ,, H44,4

*12

- - - - - - : "

. . . . . . 4--------------------------,................. 4.) 4444R21(S4210 Jdt,4 44. 4 4.....----------------------------------’.,........ ’444 4 4 4 IF W
i4
- - - - - 4---------.-------------------_4_g$4’..."_’

4!, 474(4444 (’((’4!
4(444

4 (. 4474444(’, (4(’ 4

4 4 (4 (4 u4 (4
4 4

444 414

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Table 40(2)

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. 4:4

.. ...

4.4

....4 M P

I44iZ4

GJflUO’ . ’
- 4444441 ’ 4 4., 4.1

’ ’ N’’....................... ’--"--4. ---- ’-’S .... 4 lI141i II 144 444 II1

>W. 44I ’ 44144. .... ’H’ 444’4 4’.1

4 4 II4 1 4!

. . . . ’__’ --- K> 4 4 l4(44’

... 4.4)4 I I 4
- - - - - - - - - - - - - .4.......................’...._:
ddi

. . . . . -- K.44,l,I, 1.14 4 l4444444

. 44dS 4.11L 4 4 4 4 1
- , - - -..!,44I 444 1.44,444444.

7 ----------------------------------- ’-...-’. -- 0 a I 4J 4 4 4 4!, 4,4449,4
Ul)

4ll3?i.4.lfl4 JM4. ’ 4444 44 ’1 444 4,4.4.4

...... ... ., -: ’4 ’’,’’’ g ’ >9

45 ,,.,,,’,."...............

. ’--...................... ..--.--.-..

4’!t" XCIII 4;1 I 4 44 : 1, 444, 111
4 ,

J-. ".--’.".".’.-’----"-...........4..... aIr

1 1 I 4 4+4

4,11, ,l!’ 414.14444)4

U010 j

’ J? 4’4 4 4 111,1.4 4 4 4’4 4

4.14 I’l II 444 4411444 44’II

4 1 4: 44. 14,14. 4 1, 4,

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Table 40(3)

Pt3S

ydw

<3

1J

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flflfl -4t1 l I 1 1

XJ

ddil4 1 fi. 111 ;t

fl .flfi .t,.filLfll1fl,l 1’.. ’fi.(U. II 1  1*
AT; a 01 1!. 1 1.! 1’
I l:$ 1,_

..,,...,.,... dillfi,flIl’tfl 711, --------1-------------..----......_......+._..L-------------------. ----

1 I II 1. 1 lC– fit li.l.tfifill- I fill
. -_._-...4..._..... ---------------

- - - - f---.................1...................

I1tjN. I,I fi I)4II Il.’,l, III, 11,1

0101, I

- - - - - - - - - - - I...............

I--

fi fl I I flflfi_j;1fl.Ii II I C

. . . . I..

.... 1 flfiIII II:,,
- I - - - - .

. . - fi. I
11’Ifi

flI fl

l’1Ilfl,,flII.

fl

I’3 ’3 <3

I p
p,

. . . . II-III_.._:l.1I.-._.11l-l_.lII_fiI.....,I.II.fl fl1Iifl

<3 <3 <3 <3 <3

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Table 40(4)

- 4

dd

444 iU1 I? I

tA!4zJ43

I l - I, . I I’

:--------------------------

- - - - - - - - -

.... IuJ
- -

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00 AjiAp* S.Inc

I 4 3

- St4................

. . . . . -.-.-................................. -....................

- -

. . . . - - - - ....’i..........................fl4flO4.... ----------- sr’33c410

... 1........11--- l.1l.f..4’:............
LU

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Table 41

EFFECTS OF BUPROPION HYDROCHLORIDE AND EJPROPION H’(DROBRCMIDE
IN THE EEG TRACE MONITORING
IN THE RAT

(10 RATS PERGROUP)

Lpt72 seizure cffvIt

TREATMENT NUMBER DURATION OF INITIAL SEIZURE
(mg/kg) OF
CORTEX HIPPOCAMPLIS ANIMALS
WITH
SEIZURE

ACTIVITY mean cern. mean Se.rn.

Bupropian
hydrochloride 10 33 3 25 4
100

Bupropion
hydrobromide 4 31– 6 23 2
100

Chi-Square test: ’ = p < 0.05.
#: dead (1/10).

Doses of bupropion hydrochloride (NC!) expressed in mg/kg of salt and doses of bupropion hydrobromide (HBr) expressed in mg!kg HCI molar equivalent (correction factor =1.16).

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Table 42(1)

EFFECTS OF BORROPION.YDROCHORI3E AN
N THE UG TRACE MONiTQRN
IN THE RAT

1O RATS PER GROUa
LC

BUPROF(2N&C-?000 rn!

EL ECTRiCAL SEIZURES
RAT NUMER RNN-STRUCTURE -
End urs0on

Q0320 Cftc 02:26 00:28.2
Rppocmp 02:28.8 02:51,7 00:24.9

Q0557 Crtx 00:31.9 0t:3t4
00:51.6 01:Z3 00:31.6

0022.5 00:30.4
pC3rnp0. 08:Z 06:36

Q033a Cortex 012.0 01:48I
pprnp(01200 01:40.8 00:2CM

0.342 09:10.2 00:34.9
Hippocampusi:56.36.3 0843.4 00:04:0.

Ippcampus .08:42:3 09:10.2

20543 Ctt.x .0Q20Q Q014. 00:14.8
kippcnipu 003X0 0.0:12.8 00:12.6

Codex 02.345 02.5-3.8
02.36.0 02:30.6

04.01.5 04136
ppc3mpus 04:32 041S.6

Ccrtc: .L10.5 08:21.3
ppawnpL .08:12.6 00:210

00344 Cortex 041-19.9 .00:49.0
Hcrnpi .0310.3 04:12.3 00:41.8

00:55.1

}-0ppc8mpu 05:356 08:55,5

20546 Cortex 05251 04:11.5 00:36,5
Kppocampu 03.25.1 04:11.3 00:354

08.39.0
ipompus .08:39.3 03:00.8

20348 Qwex 03:55.0 0333.2 00:35.2
IOppooarnpu9 .02:50,9 025$ 0530.8

20549 Cortex: .04:0.3.6 04:57.0 00:35.2
Hippocampus04:08.7 - 0435.1

20351 01:383 0138.0 00:26.6
)-I1ppocempu 01:39.4 01:35.6 00:16,4
Mean 00:322 00:24.6

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Table 42(2)

EFFECTS OF B(JPROPtON HYOROCHLORIDE AND BUPROPON HYDROBROMDE N THE EEG TRACE MONITORING
N THE RAT

(W RA7$ PER CROJ

LgJiw/J&

BU PRO PION HBr (100 mO/}g)

ELECTRICAL SEIZURES
RAT NUMBER BRAIN STRUCTURE
Begin End Duration

003.52 Cortex 01:47.7 02:04.6 0018.9
HiPPQCrnPU 01:48.1 02:04.8 00:16.7

Q0353 Cortex 00:15.0 00:53.7 00:38.8
- ppocampus 00:24.8 00:48.6 00:23.8

00354 Cortex 01:47.5 02:14.1 00:26.5
Hppocmpu 01:49.9 02:14.5 00:24.7

0030 Cortex 04:11.4 04:53.8 00:42.3
Hippooempus 04:14.2 04:39.5 00:25.3
Mean 00:31.1 00:22.6

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CLAIMS

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1. A composition comprising bupropion hydrobromide and at least one pharmaceutically acceptable excipient;
wherein administration of an amount of a bupropion hydrobromide to a first rat results in less incidences of and/or less severe bupropion-induced seizures when compared to incidences of and/or severity of bupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity of bupropion-induced seizures are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode.

2. The composition of claim 1, which is in tablet form.

3. The composition of Claim 1, which is a modified release formulation.

4. The composition of Claim 1, which is in tablet form and wherein the bupropion hydrobromide is contained within a core of the tablet further comprising a coating over the

core.

5. The composition of Claim 4, wherein the coating is a controlled release coating.

6. A. composition comprising bupropion hydrobromide and at least one pharmaceutically acceptable excipient;
wherein administration of about 100mg/kg of a bupropion hydrobromide to a first rat results in less incidences of and/or severity of bupropion-induced seizures when compared to incidences of and/or severity of bupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity of bupropion-induced seizures are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode,

7. A method oftreating a subject at risk of bupropion-induced seizures in need of bupropion treatment, the method comprising:

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administering a composition comprising bupropion hydrobromide to said subject in an amount sufficient to treat said subject.

8. The method of Claim 7, wherein the composition comprises an amount of bupropion hydrobromide chosen from 174mg, 348mg and 522mg.

9. The method of Claim 7, wherein the composition is in tablet form and the administering comprises oral administration.

10. The method of Claim 7, wherein the composition is a modified release formulation.

11. The method of Claim 7, wherein the composition is in tablet form and wherein the bupropion hydrobromide is contained within a core of the tablet further comprising a coating over the core.

12. The method ofClaim 7, wherein the coating is a controlled release coating.

13. A method ofreducing incidences of bupropion-induced seizures comprising: administering a pharmaceutically effective amount of bupropion hydrobromide to a subject in need of bupropion administration;
wherein incidences of bupropion-induced seizures resulting from the administration of bupropion hydrobromide is less than incidences of bupropioninduced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride.

14. The method of claim 13 wherein bupropion-induced seizures resulting from the administration ofbupropion hydrobromide is less severe than bupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride.

15. A method ofreducing incidences of bupropion-induced seizures comprising: administering a pharmaceutically effective amount of bupropion hydrobromide to a subject in need of bupropion administration;
wherein administration of about 100mg/kg ofthe bupropion hydrobromide to a first rat results in less incidences ofbupropion-induced seizures when compared to incidences of

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bupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of bupropion-induced seizures in the ’first and second rats are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode.

16. A method ofreducing the incidences of bupropion induced seizures comprising coadministration of a bromide salt with a bupropion salt, wherein the bromide salt is administered in an amount of less than about 3.5 mg/kg.

17. The method of claim 16 wherein the bromide salt is sodium" bromide.

18. The method of claim 16 wherein the bupropion salt is bupropion hydrochloride.

19. A composition comprising bupropion hydrobromid.e and at least one pharmaceutically acceptable excipient;
wherein administration of about 100mg/kg of a bupropion hydrobromide used to manufacture the composition to a first rat results in less incidences of and/or severity of bupropion-induced seizures when compared to incidences of and/or severity of bupropion-induced seizures resulting from administration of an equivalent molar amount of bupropion hydrochloride to a second rat; and
wherein the incidences of and/or severity of bupropion-induced seizures are measured by an electroencephalogram analysis using a hippocampally implanted depth electrode.

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FIG. 21

RAag,vo’L" Nur..nb*r of ConvulWana Using Mfld Ntras

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.i m..

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t4C
- + 0

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I
110 14.41 010 6072 Mo KAW

FIG. 32

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7PKi021 323O)
Mean eyStt* P14ams 8urGp1* 14

pmp

Ti

4 . 12

FIG-33 M*a C&’T Pk tbt

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Study 864PØ121 23Ø1
M*n steady $t* p*Ern
Hydrybpoeo Cot n38)

4 8 12.

TIM* 4t

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FIG. 34 wan Thm Tim Plot fw Sty 75K (3)

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Sndy PK11Zi 33O)
MOOM Wmady Stft Masms flprpon Thrm1O Joho C n*ron:n*3)

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4 20. 24

TIMO (HOW)

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ai Sto*dy State Pama Supmplon
Wbmsoflno Akctwl Cros

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4. 12 10 20 2.4

TWO’ł)

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SWO plaw-4 pharmowioutcal.
Mtty fttghtod 4n

VW XL34
> Td

. 412 114 14,10 24

PIG, 31 MA
m1y

gtod C AWc.-The. PIW
trn21 (2O)

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(322
Mom SlagWOM, Rama BwnC ubon&

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24 -48 rz G 10 144
Tmt

FtC, 38 p S-L2M WI

S (fl)

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EMS

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Study BO 5P1Gth 22
Mean 5 Pmsma supmolon Con iations (nz4)

0 4 1:2. 1

Ifte

FtG 39)AVO;c TmI9Mfor Study
(22) Only Datapoiam From O - 36 Ui

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$tU: 87P10121 (3228)
Plasma

dr*xybupropkn on

t’...2 x

i.4 48 72 94 Zł 144 18 192 216

Thrs.. LHW)

RG, 40 piwmIyd ntt The:kt fr wdy flfl2.1 t22)

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’FIG. 41
21 (32,!K

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Study (22
1sma urkn

- *--Ix o"r."’loo1r A 114
IXL

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43 72 & ’120 144 :Ift 12 21, rw

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Study B .K..10121
an SIng* E Plasm Bupmptoo
F-rift"ralno Akthoi ConwntrOms jh*46)

XL 04T$

24 40 72 144 18 1*2 21

$2 Mt
1.0 121

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iudr $4O Z)
Moon.Shi1:O1s Plam-a Pflk1Jk.
ActMty WakgMod

24 40 72 9 120 144 10 IQ. 216

FIG. 43 M Mi (MWCflme?kt (%)

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$t*. 9011i54PK$i2i flZ
Mom. Single DePlasma. Buproptn n483

+!. son Ti QC1*I 1ad

24 46 72 ’N ’IZO 144 148 210

FIG.. 44 ’M i. CiE-T Tht t

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ISO

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322

Moon: $rg Ooe Fl"ma Buprupiat QmwtmtWs irr-40),

n m F
. 3(_ X34 ovTwoolLC

0

2

4 Q 1

11G. 45 cit’rMot.fir $y80,04,50Kl,24 2)- Only oltvdiftFtm c

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ftdy (322)
Młan Single Cass Pin H xybuppon CrU (n4)

OB

C 24 49 U iG 44 Ift M 214

FIG. $6:Mn Pi yupr Mot
w12 C29)

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S. RO8754P1Oi1 (22
MW Dose Plasm
Thrwamhw khOL Uenfr1IGflR (fld48)

*43 4
- 0- impmom HWXL:30

24 4 72 90 120 144 16 192 214

flM

FIG, 47 Mx flp1 Th iht c-iPlotfix. Sudy
T$?X4Mfl (229;

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:15P16131 3ZW

Mr o 004Pkii kpv*pgn
Cone f’. (n4}

.24 7 20 ’144 160 fl 2-10

That H*jr

. FK.. 48!, P up$ &,ytummi ft sQ6754PKAOIZ (329

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*tsdy 4P1O121 3Z::
Oo

 MWT ornp*, 4i4

4Mmpmpkm t4æ k
.o+..

2$ 12 125 j$ Im. 1*2 214

flnI.1$ot)

FIG, 49 Plwms Phw=*wl4mJ AaMty WoOW Cp A..C>Tn Mt lbr: y754P.iG121

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iW Mut O*Fn
Mei Plasma Bprncoirimumflom tim=Ml

WkXLW Tk LO$1P
XL

4 3 24

TMW (Hours)

FIG. 50 Mg*c BmpMi. Plot FOf Sady (AA4t)

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7,40.0

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Two-Way WVpW-D*" F*rg $tud
Mm Pa ii1*in 2)

. 4- rnTa
. . >

4 1246 .20 24

1flm*

FIG.mm ik Plot For Study 12J AMOS)’

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W*yMu1tIpIł4o istng ady
Msân r1m pO$Q ThTHo Qh0 ()

1400:

0+
0

. 4- 3p
3

.4 * 12 24

. ttØ

E.IG..2

B2PK4fl. (AA40-5$)

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Two-way tin study
Own PLasma pro’ Erh AWbØJ GamohlrOom

Z44,

Is

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TWoW1, .. 5tuy

M* Mum i*nnoe..*.1*y Wul,. cp$t (nZ)

. 4 a 12 14 24’

FIG. 54 M .MWtdcFAWcThP.

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TITULO DE LA INVENCION
BROMHIDRATO DE BUPROPION Y APLICACIONES TERAPEUTICAS

5 SOLICITUDES RELACIONADAS

Esta solicitud reivindica la prioridad de la Solicitud de los Estados Unidos No. de Serie 11/834.848, presentada el 7 de agosto de 2007. Esta solicitud es una continuación en
parte de la Solicitud de los Estados Unidos No. de Serie 11/751.768, presentada el 22 de mayo de 2007, actualmente pendiente; y una continuaciOn en parte de la Solicitud de los
10 Estados Unidos No. de Serie 11/755.946 presentada el 31 de mayo de 2007, siendo
ambas continuaciones de la Solicitud de los Estados Unidos No. de Serie 11/475.252, presentada el 27 de junio de 2006, ahora U.S. 7.241.805; y reivindica la prioridad de la Solicitud Provisional de los Estados Unidos No. de Serie 60/693.906 presentada el 27 de

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junio de 2005. La totalidad de la Solicitud de los Estados Unidos No. de Serie
11/751.768, Solicitud de los Estados Unidos No. de Serie 11/755.946, U.S. 7,241,805, y Solicitud Provisional de los Estados Unidos No. de Serie No. 60/693.906 se incorpora a
la presente a modo de referencia.

CAMPO DE LA INVENCION

20 La presente invención se refiere a bromhidrato de bupropion y a formulaciones de
bromhidrato de bupropion, asi como tambiºn a su uso para el tratamiento de afecciones
(por ejemplo, trastorno depresivo mayor, trastorno del humor con depresión bipolar, otros trastornos del humor, trastornos de ansiedad, trastorno de ansiedad generalizada,
trastorno de pªnico, trastorno por estrØs postraumÆtico, adicción a la nicotina, obesidad,
’ 25 trastorno de deficit atencional con hiperactividad, sIndrome de las piernas inquietas,
disfunción sexual y trastornos afectivos estacionales).

ANTECEDENTES

El bupropion es un antidepresivo conocido. El mecanismo neuroqulmico del efecto
30 antidepresivo del bupropion no se conoce bien. El bupropion afecta a los productos
qulmicos dentro del cerebro que los nervios usan para enviarse mensajes entre si. Estos mensajeros qulmicos se Haman neurotransmisores. Los neurotransmisores que son liberados pot los nervios son retomados por los nervios que los liberan para su
reutilización (esto se denomina recaptación). Muebos expertos creen que la depresión es
35 causada por un desajuste entre las cantidades de neurotransmisores que se liberar. El
bupropion es un inhibidor selectivo de la recaptación de la catecolamina (dopamina y norepinefrmna) y funciona inhibiendo la recaptación de los neurotransmisores de
dopamina y norepinefrmna, una acción que resulta en mÆs dopaminay norepinefrmna

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disponibles para transmitir mensajes a otros nervios. Su efecto sobre el mecanismo de recaptación de la serotonina es muy pequeflo o nub. En consecuencia, el bupropion es
ü nico en que su efecto principal es sobre la dopamina, un efecto que no es compartido
por los inhibidores selectivos de la recaptación de la serotonina (ISRS), por ejemplo, la paroxetina (PAXILfi), la fluoxetina (PROZACfi), la sertralina (ZOLOFTfi)) ni los antidepresivos triciclicos o ATC, por ejemplo, la aniitriptilina (ELAVILfi), la
imipramina (TOFRANILfi) y la desipramina (NORPRAMIIfi).

El bupropion tambiØn puede utilizarse para tratar otras afecciones, cuyos ejemplos no
10 limitantes son la adicción a la nicotina (por ejemplo, el abandono del hÆbitode furnar), ci
aumento de peso (por ejemplo, la obesidad), la enfermedad de Parkinson y tin trastorno afectivo estacional.

El clorhidrato de bupropion se encuentra comercialmente disponible en forma de
15 liberación inmediata (WELLBUTRINfi), en forma de liberaciOn sostenida
(WELLBUTR1Nfi SR y ZYBANfi) y en forma de liberaciOn extendida
((WELLBUTR]INfi XL). Tanto WELLBUTRINfi SR como ZYBANfi son qulmica y famiacØuticarnente idØnticos. WELLBUTRINfi, WELLBUTRJ4fi SR y
WELLBUTRINfi XL cimnicarnente para ci tratamiento de trastorno depresivo
20 mayor, trastorno del humor con depresiOn bipolar, otro trastorno del humor, trastornos de
ansiedad, trastorno de ansiedad generalizada, trastorno de pÆnico,trastorno por estrØs postraumÆticoy trastornos afectivos estacionales y ban sido aprobados para us uso en el tratamiento de trastorno depresivo mayor. ZYBANfi Se aprobO como una ayuda para los
40 pacientes que quieren dejar de fumar. WELLBUTR[Nfi, la formulación de bupropion de
25 liberación inmediata, se administra tres veces at dIa, adecuadamente con 6 o mÆs horas
entre las dosis. Para los pacientes que requieren mÆs de300 mg de bupropion por dia, se
indica que cada dosis no debe exceder de 150 mg. Esto requiere una administración de
los comprimidos at menos 4 veces at dia con at menos 4 horas entre las dosis. La
formulación de liberación inmediata resulta en una liberación mayor at 75% de bupropion
30 en el medio de disolución en 45 minutos. Los productos de liberación sostenida se
administran dos veces at dia y los productos de liberación extendida se administran una
vez at dia.

El uso de bupropion para ci tratamiento de enfermedades y afecciones presenta algunas
35 ventajas. Por ejemplo, el bupropion no inhibe la monoamina oxidasa y no bboquea
significativamente la recaptación de serotonina, a diferencia de otros inhibidores de la recaptaciOn de monoamina neuronal. Por to tanto. la administración de bupropion puede

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evitar o disminuir muchos de los efectos adversos comnmente asociados a otros antidepresivos tales como agentes tricIclicos e inhibidores de la monoamina oxidasa.

Uno de los principales efectos secundarios conocidos del bupropion es la incidencia de
5 crisis convulsivas (por ejemplo crisis convulsivas epilØpticas del gran ma!), que se sabe
estÆmuy relacionada con la fuerza de la dosis del bupropion. Por ejemplo, con WELLBUTRINfi con la dosis originalmente recomendada (400-600 mg), se encontró
que la incidencia de crisis convulsivas en los pacientes tratados con el fÆrmaeo fue sustancialmente mayor que con otros antidepresivos, por lo que en 1986 el fÆrmacofue
10 retirado del mercado. Se demostró que el riesgo de crisis convulsivas aumentó
sustancialmente entre la dosificaciOn de 450 mg/dIa y la dosificación de 600 mgldIa.
Como resultado, el bupropion Se volvió a introducir en el mercado en 1989 con una dosis maxima de 450 mgldia. Sin embargo, se ha documentado que las crisis convulsivas se producen en pacientes que toman bupropion no solamente en sobredosis, sino tambiØn en
15 dosis consideradas terapØuticas (es decir, 450 mg/dIa o menos) [Pesola & Avasarala,
Bupropion seizures proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department, J. Emerg.Med. 2002, 22, 235-239.] Las altas concentraciones de bupropion necesarias para la eficacia (por ejemplo, eficacia
como antidepresivo) establecen una concentración de base alta y, por lo tanto, se crea un
20 marco para un Indice terapØutico estrecho a la luz del riesgo dependiente de la
coneentración de causar crisis convulsivas. [Preskorn S., Bupropion: What Mechanism
of Action? J. Practical Psychiatry and Behavioral Health, Jan. 2000, 272-276.1

Se sabe que el bupropion disminuye el umbral de crisis convulsivas y se ha citado como
 25 una de las principales causas de crisis convulsivas relacionadas con fannacos [en tercer
lugar detrÆsde las crisis convulsivas por intoxicación por cocalna y por abstinencia de benzodiazepinas Davidson J., Seizures and Bupropion: A Review, J. Clin.Psychiatry,
1989, 50, 256-61.]. Se sabe que el bupropion solo o en combinación con otros
medicamentos induce a crisis convulsivas en algunos pacientes sin antecedentes de
30 actividad de crisis convulsivas. No es infrecuente que los pacientes reciban tratamiento
con otros medicamentos antidepresivos y/o antipsicóticos ailpicos en combinación con el bupropion. Por lo tanto, existe la necesidad de controlar, reducir o eliminar las
incidencias de crisis convulsivas que resultan de la administración de bupropion, ya sea
solo o conjuntamente con otros medicamentos proclives a reducir ci umbral de las crisis
35 convulsivas. TambiØn se sabe que el bupropion produce crisis convulsivas conjuntamente
con fÆrmacos no recetados (recreativos), tales como cocalna y alcohol.

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La selección de una sal adecuada para un fÆrmacocandidato es reconocida como un paso importante en la fase precilnica del desarrollo de un fÆrmaco.Cambiar la forma sauna de
un fÆrmacoes un medio reconocido de modificar sus propiedades qulmicas y biológicas
sin modificar su estructura. La elección de una sal en particular puede tener un marcado
5 efecto en las propiedades fisicoqulmicas del fÆrmaco(por ejemplo, la velocidad de
disolución, solubilidad, estabilidad e higroscopicidad). La sustitución de una forma
sauna de un fÆrmaco por otrapuede alterar la eficacia terapºutica, la seguridad y/o la calidad, que son fundamentales para la fonnulación optima de la forma farmacØutica y la fabricación a gran escala. Sin embargo, hasta ahora, no hay manera fiable de predecir
10 exactamente quØ efecto tendrÆcambiar la forma sauna de un fÆrmacoactivo sobre su
actividad biolOgica. MÆs aun, inclusoluego de haberse preparado muchas sales del
mismo agente bÆsico, noexisten tØcnicas de detecciOn sistemªtica para facilitar la
selecciOn de la sal que mÆsprobablernente exhiba los perfiles farmacocinØticos, de solubilidad y de formulación deseados. En resumeri, no existe una forma confiable de
15 predecir la influencia de una especie de sal en particular sobre el comportamiento del
compuesto base en las formas farrnacØuticas. [Berge et al., Pharmaceutical Salts, Journal Pharm. Sci., 1977, Vol.66, No. 1; Verbeeck et al. Generic substitution: The use of
medicinal products containing different salts and implications for safety and efficacy, EP Journal Pharm. Sci, 28, 2006, 1-6.] La decision de cambiar la forma salina en una etapa
20 posterior introduce la necesidad de repetir las pruebas toxicolOgicas, de formulación y
estabilidad, con las implicaciones obvias para el desarrollo general y tiempo de
producción para el nuevo producto farmacØutico.

9 De acuerdo con la base de datos del CASfi ("Chemical Abstracts Registry"), a la fecha
25 de esta solicitud, las ünicas otras sales de bupropion de las que se ha informado
previamente son las sales de clorhidrato (HC1), (2Z)-2-butenodioato, (2E)-2-
butenodioato, metanosulfonato, Æcido fOrmico,2-hidroxi- 1,2,3 -propanotricarboxilato,
fosfato y de trifluorometanosulfonato.

30 El bromuro de sodio y el bromuro de potasio son sales que se utilizaron ampliamente
como anticonvulsivos y sedantes a fines del siglo XIX y comienzos del siglo XX. Su
acciOn se debe al bromuro. A la fecha de esta solicitud, el bromuro no ha sido
aprobado por la AdministraciOn de Alimentos y FÆrmacosde los Estados Unidos (FDA) para su utilización en hunianos para controlar crisis convuisivas. Sin embargo, en
35 Alemania, sigue estando aprobado su uso como fthmaco antiepileptico en humanos, en
particular niflos y adolescentes (cornercializado con la marca DIBRO-BE MONOfi). Las indicaciones incluyen forrnas graves de crisis convulsivas tónico-clónicas generalizadas,

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crisis convulsivas del gran mal relacionadas con la infancia temprana y tambiØn crisis convulsivas mioclónicas graves durante la infancia. Un comprimido contiene una dosis terapØutica de 850 mg de bromuro de potasio. El bromuro fue el primer fÆrmaco que se encontró era eficaz para el tratamiento de la epilepsia en humanos. El bromuro tambiØn
se ha utilizado como fÆrmaco veterinario, por ejemplo, como medicaciOn antiepilØptica
para perros y gatos.

Se han reportado niveles de dosis terapØuticas de bromuro para tratar la epilepsia. Para adultos, una dosis normal reportada varia de 3-6 gramos/dia [Niedermeyer E., ed.
10 Benzodiazepines and other antiepileptic drugs, In: The epilepsies: Diagnosis and
management, Baltimore: Urban & Schwarzenberg, 1990, 311-2; Ryan and Baumann; Bromides in Epilepsy Treatment, Pediatr Neruol, 1999, 21; 523-528.]. Para niæos
menores de 6 afios se han recomendado niveles de dosis de 600-1800 mg/dIa en dos o tres dosis. Para ninos mayores de 6 aæos se ha recomendado administrar 300 mg a 1 gramo
15 tres veces por dIa. [Dreifuss F.E. and Bertram D.I-L, Bromide therapy for intractable
seizures, Epilepsia, 1986, 27; 593.; Ryan and Baumann; Bromides in Epilepsy Treatment, PediatrNeruol, 1999, 21; 523-528.]. Se ha informado que laDE5O (dosis efectiva
mInima requerida para producir un efecto deseado en el 50% de la población de prueba)
para el bromuro contra crisis convulsivas inducidas qulmicamente (con pentilenotetrazol)
20 en ratones es de 910 mg/kg [J.S. Grewal et al., Journal of Pharmacology and Expt’l
Therapeutics, 1954, Vol. 112, Issue 1, 109-115.]

El bromuro fue el anticonvulsivo mÆs utilizadohasta la introducción del Fenobarbital en
1912 y otros anticonvulsivos mÆs seguros. Se descubrió posteriormente que los niveles
 25 de dosis terapØuticos de bromuro conocidos provocaban bromismo y varios otros efectos
tóxicos significativos. El Indice terapØutico conocido es muy pequeflo para el bromo. Al
igual que con otros anticonvulsivos, a veces incluso las dosis terapØuticas provocan
intoxicación. A menudo indistinguibles de los efectos secundarios ’esperados", estos
efectos tOxicos pueden incluir: bromismo (es decir, reacciones del sistema nervioso
30 central que van de sonmolencia a coma, caquexia, exicosis, pØrdida de reflejos o reflejos
patologicos, crisis convulsivas clónicas, temblores, ataxia, pØrdida de sensibilidad neural, parÆlisis,edema de papila de la vista, habla anormal, edema cerebral, delirio manifiesto, agresividad, psicosis); pØrdida de apetito; nÆusea/emesis; letargo;propensión a dormir durante el dIa; depresión; pØrdida de concentración y memoria; confusiOn; dolor de
35 cabeza; y enfermedades de la piel, tal como dermatitis en forma de acne.

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El mecanismo de acciOn exacto del bromuro es desconocido. No se ha establecido el mecanismo farmacolOgico de las crisis convulsivas inducidas por bupropion ni la utilidad
de los frrnacos antiepilØpticos (por ejemplo, ci bromuro) en el tratamiento de dichas
crisis convulsivas. Existe un conocimiento limitado acerca de la eficacia de los fÆrmacos
5 antiepilØpticos en las crisis convulsivas inducidas por bupropion en ratones [P.Tutka et
al., Epilepsy Research 64, 2005, 13-22.], y no se sabe nada acerca de la eficacia del
bromuro para controlar crisis convulsivas inducidas por bupropion. Si bien no se han
lievado a cabo estudios formales para determinar los rangos de dosis terapØuticas para la eficacia del bromuro contra las crisis convulsivas inducidas por bupropion, se conocen
10 los rangos de dosis terapØuticas para la eficacia del bromuro contra otras crisis
convulsivas conocidas. Por ejemplo, se sabe que el nivel de dosis terapØutica para el brornuro contra las crisis convulsivas inducidas por pentilenotetrazol es de 910 mg/kg
[M.S. Grewal et al., Journal of Pharmacology And Experimental Therapeutics, Vol. 112, Issue 1, 109-115, 1954]. Para otros varios fÆrmacos antiepilØpticos (porejemplo,
15 clonazepam, vigabatrina, etosuxirnida, vaiproato), los niveles de dosis terapØutica
necesarios para el tratamiento de crisis convulsivas inducidas por bupropion son comparables a los niveles de dosis necesarios para el tratamiento de crisis convulsivas inducidas por pentilenotetrazol en ratones. [P. Tutka et al. Epilepsy Research 64 (2005) 13-22; J.J. Luszczki,, 2005, 30, 958-973; J.A. Armijo et al. Pharmacological Res. 2005,
20 51, 489-496; K.K. Borowicz etal. Epilepsia, 2004, 45(10), 1176-1183; S.J. Czuczwar et
al., Polish Journal of Pharmacology, 2003, 55, 363-370; P. Tutka et al., J. Neural Transmission, 2002, 109, 455-466; K.K.Borowicz et al. European Neuropsychopharmacology 2004, 14, 77-85; and K.K.Borowicz et al., Polish Journal of Pharmacology, 2004, 56, 187-193.]
 25

Sigue existiendo la necesidad de una composición de bupropion que pueda utilizarse para
el tratamiento y/o la prevención de una afección (por ejemplo, un trastorno depresivo
mayor y la adicción a la nicotina) en sujetos que puedan beneficiarse de la administración
de bupropion, y que puedan proporcionar una menor incidencia y/o reducir la gravedad
30 de las crisis convulsivas asociadas a la administración de bupropion, en comparación con
las composiciones de bupropion conocidas.

El desarrollo de una formulación de bupropion estable que se administre una vez al dIa
con liberación modificada y que tenga niveles seguros de la sal bromhidrato de
35 bupropion, y que reduzca la incidencia y/o la gravedad de las crisis convulsivas inducidas
por bupropion en comparación con otra composición por lo demªs similar o iddntica que

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contenga una cantidad molar equivalente de clorhidrato de bupropion constituirfa un avance en la tºcnica.

DESCRIPCION

Ciertas realizaciones de la presente invención se refieren a una composición de bupropion que comprende una cantidad farmacØuticamente efectiva de bromhidrato de bupropion;
en donde la composición inesperadamente produce menos incidencias de crisis
convulsivas yio crisis convulsivas menos graves asociadas a la administración de
bupropion que una composición por Jo demÆs similar oidØntica que contenga una
10 cantidad molar equivalente de clorhidrato de bupropion.

Ciertas realizaciones de la invenciOn se refieren a una composición de bupropion que comprende una cantidad segura y farmacØuticamente efectiva de bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable; en donde la
15 administración de una cantidad de bromhidrato de bupropion a una primera rata resulta
inesperadamente en menos incidencias y/o reduce la gravedad de crisis convulsivas inducidas por bupropion en comparación con las incidencias de crisis convulsivas
inducidas por bupropion que resultan de la administración de una cantidad molar
equivalente de clorhidrato de bupropion a una segunda rata; y en donde las incidencias
20 y/o la gravedad de las crisis convulsivas inducidas por bupropion se miden mediante un
anÆlisisde electroencefalograma utilizando tin electrodo profundo implantado en el
hipocampo.

Ciertas realizaciones de la presente invención se refieren a una composiciOn de bupropion
925 que comprende una cantidad farmacØuticamente efectiva de bromhidrato de bupropion;
en donde dicha composición inesperadamente produce menos incidencias de crisis
convulsivas y/o crisis convulsivas menos graves asociadas a la administración de
bupropion y es mÆs estableque una composición por lo demÆssimilar o idØntica que
contenga una cantidad molar equivalente de clorhidrato de bupropion. En particular,
30 dicha composición de bromhidrato de bupropion es mÆs estable queotra composición por
lo deinÆssimilar o idØntica que contenga una cantidad molar equivalente de clorhidrato
de bupropion en ciertas condiciones de almacenamiento (por ejemplo, cuando se
almacena durante 3 meses o 6 meses a 40°C y con un 75% de humedad relativa), como se demuestra por una cantidad reducida de al menos una porciOn (por ejemplo, producto de
35 degradacion) que es caracterIstica de la degradacion del bupropion y/o una fiuctuaciOn
reducida o reducción en la potencia luego de almacenarse en condiciones de
almacenamiento aceleradas (por ejemplo, luego de alniacenar durante 3 meses o 6

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meses), y/o una fluctuaciOn reducida del perfil de disolución in vitro en el menos un rnedio de disolución durante un perlodo de 24 horas.

Ciertas realizaciones de la presente invención se refieren a mØtodos para reducir las incidencias de crisis convulsivas inducidas por bupropion y/o reducir la gravedad de las
crisis convulsivas inducidas por bupropion que comprenden administrar una cantidad
segura y farmacØuticamente efectiva de bromhidrato de bupropion a un sujeto que
necesita la administración de bupropion, en donde dichas incidencias y/o gravedad de
crisis convulsivas inducidas por bupropion que resultan de la adrninistración de
10 bromhidrato de bupropion son menores que las incidencias y/o gravedad de crisis
convulsivas inducidas por bupropion que resultan de la administración de una cantidad
molar equivalente de clorhidrato de bupropion.

Ciertas realizaciones de la presente invención se refieren a mØtodos para tratar una
15 afección que comprenden administrar una cantidad segura y efectiva de bromhidrato de
bupropion a an sujeto que necesita la administración de bupropion, en donde el
bromhidrato de bupropion produce menos incidencias de crisis convulsivas inducidas por bupropion que una cantidad molar equivalente de clorhidrato de bupropion.

20 Ciertas realizaciones de la presente invención se refieren a mØtodos para tratar una
afección que comprenden administrar una cantidad segura y efectiva de brornhidrato de bupropion a un sujeto que necesita la administraciOn de bupropion, en donde el
bromhidrato de bupropion produce menos incidencias de crisis convulsivas inducidas por bupropion y/o reduce la gravedad de dichas crisis convulsivas con respecto a una
25 cantidad molar equivalente de clorhidrato de bupropion.

Como se demuestra mÆsadelante, el bromhidrato de bupropion tiene una menor
propensión a inducir crisis convulsivas y/o a reducir la gravedad de las crisis convulsivas inducidas por bupropion en comparación con el clorhidrato de bupropion. Esto permite
30 reducir las incidencias de dichas crisis convulsivas, reducir la gravedad de las crisis
convulsivas, tratar sujetos que de otra forma no serfan candidatos para la terapia con bupropion debido a su riesgo de inducción de crisis convulsivas, y/o tratar un sujeto con dosis incluso mÆs altasde bupropion de las que serian posibles y seguras con clorhidrato
de bupropion.
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Ciertas realizaciones de la presente invención se refieren a mØtodos para tratar una
afección que comprenden administrar una composición que contiene una cantidad segura

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y efectiva de bromhidrato de bupropion a un sujeto que necesita la administración de bupropion, en donde el bromhidrato de bupropion produce menos incidencias de crisis convulsivas inducidas por bupropion que una cantidad molar equivalente de clorhidrato
de bupropion.

Ciertas realizaciones de la presente invención se refieren a un mØtodo para tratar an
sujeto con riesgo de crisis convulsivas inducidas por bupropion que necesita dieho tratamiento mediante la administración de una cantidad segura y efectiva de bromhidrato
de bupropion al sujeto.
10

Ciertas realizaciones de la presente invención se refieren al uso de composiciones de bromhidrato de bupropion para preparar un medicamento para el tratamiento de una o
mÆs afeecionesque pueden beneficiarse de la administración de bupropion, en donde el

16 tratamiento permite reducir o evitar las incidencias y/o reducir la gravedad de las crisis
15 convulsivas inducidas por bupropion en comparación con una composición por lo demÆs
similar o idØntica que contenga una cantidad molar equivalente de clorhidrato de
bupropion.

Ciertas realizaciones de la presente invención contemplan, ademÆs, un mØtodo para
20 preparar un medicamento para el tratamiento de una afeceión que se puede beneficiar de
la administración de bupropion que comprende poner en contacto una cantidad eficaz de bromhidrato de bupropion con uno o mÆsexcipientes farmacØuticamente aceptables.

Ciertas realizaciones se refieren al uso de sales de bromuro para reducir las incidencias
1025 y/o la gravedad de crisis convulsivas inducidas por bupropion, tales como las crisis
convulsivas inducidas por la administración de clorhidrato de bupropion.

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Ciertas realizaciones se refieren a composiciones que comprenden un compuesto de
fOrmula I (bromhidrato de bupropion):

0
Cl

’C(CH3)3 (I)

y portadores, excipientes y/o diluyentes farmacØuticamente aceptables; teniendo dicha composición una estabilidad mayor que una composiciOn farmacØutica correspondiente
35 que comprende clorhidrato de bupropion y portadores, excipientes y/o diluyentes

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farrnacºuticamente aceptables; y reduciendo o evitando las incidencias y/o reduciendo la gravedad de crisis convulsivas inducidas por bupropion.

En ciertas realizaciones de la presente invención, la sal de bupropion puede estar en
5 forma de sus formas anhidras, hidratadas y solvatadas, en forma de profªrmacos y en los
enantiómeros individual y ópticamente activos de la sal de bupropion, como por ejemplo (+)-bupropion y (-)-bupropion. Las sates de bupropion farmacØuticamente aceptables adecuadas Para su uso en la presente invención son mÆs estables que el clorhidrato de bupropion, y reducen o evitan las incidencias de crisis convulsivas asociadas a la
10 administraeión de bupropion. Las sales de bupropion adecuadas tambiØn incluyen por
ejemplo, las sales de adición de Æcido farmacØutieamenteaceptables. En ciertas realizaciones, la sal de adición de Æcido de bupropion se puede obtener indirectarnente mediante la adición por separado de bupropion y un Æcido a la formulaciOndel nücleo.

15 Ciertas realizaciones de la presente invención contemplan el uso de brornhidrato de
bupropion Para preparar un medicamento Para tratar una afección que puede beneficiarse
de la administración de bupropion, en donde dicho medicamento tiene una mayor
estabilidad que un medicamento correspondiente que comprende clorhidrato de
bupropion, y reduce o evita las incidencias yio reduce la gravedad de las crisis
20 convulsivas asociadas a la administración de bupropion.

Segün se trata mÆs adelante y se conoce en general en ci area, el medio de disolución y
las condiciones adecuadas Para analizar las caracterIsticas de disolución de las formas

farmaeØuticas corno los comprimidos son bien conocidos por los tØcnicos en la materia y
25 estÆncontenidos en la farmacopea de los Estados Unidos y sus contrapartes europea o
japonesa e incluyen, a modo de ejemplo, el aparato tipo 1 de disolución de la USP
(MØtodo de la Cesta Rotatoria) en 900 ml de agua; HC1 0,1 N; HCI 0,1 N + Cetrimida
0,1%; soluciOn amortiguadora de la USP de pH 1,5; solución amortiguadora de acetato de
PH 4,5; solución amortiguadora de fosfato de pH 6,5; o soluciOn amortiguadora de
30 fosfato de pH 7,4 a 75 RPM a 37°C +b- 0,5°C. AdernÆs,otros ejemplos de medios de
disolución apropiados incluyen los medios de disoluciOn USP-3 y las condiciones de disoluciOn USP-3, por ejemplo, LGS de pH 1,2; solución amortiguadora de acetato de pH
4,5 y solución amortiguadora de fosfato de pH 6,8.

35 Ciertas realizaciones de la presente invención contemplan el uso de brornhidrato de
bupropion Para producir comprimidos que se pueden administrar una vez al dia u otras formas farmacØuticas que son bioequivalcntes, segün definen los criterios de la FDA, a

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los comprimidos de WELLBUTRINTM0 ZYBAN/WELLBUTR1NTM SR cuando se administran una vez a! dia a un sujeto que lo necesita. En particular, a! menos uno de TmÆx, Cmx operfil de AUC de ciertas realizaciones de la presente invenciOn estÆn
dentro del 80% al 125% de los de WELLBUTRINTM y ZYBANTM/WELLBUTR[NTM
5 cuando se administran una vez al dIa a un sujeto que lo necesita. En ciertas realizaciones,
estas formulaciones tambiØn carecen de cualquier efecto importante por el consumo de alimentos.

Ciertas realizaciones de la presente invenciOn proporcionan formas farmacØutieas de
10 bromhidrato de bupropion (por ejemplo, comprimidos) que contienen al menos un
recubrimiento (por ejemplo, el recubrimiento SMARTCOATTM) que es resistente a la absorción rÆpida de la dosis en un alto contenido de alcohol, (por ejemplo, etanol al
40%), en donde las formas farmacØuticas permiten reducir o evitar incidencias yb
reducir la gravedad de las crisis convulsivas inducidas por bupropion.
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Ciertas realizaciones de la presente invención incluyen medicamentos tanto orales como
no orales que contienen bromhidrato de bupropion. For ejemplo, la invenciOn abarca composiciones adecuadas para la administración oral, tópica, inyectable, por inhalación u
otras formas de administración.

Ciertas realizaciones de la presente invención incluyen fornrnlaciones de liberación
extendida, foimulaciones de liberaciOn retardada y/o formulaciones de absorción
mej orada.

025 En una implementaciOn mÆs particularde ciertas realizaciones de la invención, una
composición de un medicamento de bupropion comprende (i) ffli nücleo que incluye broinhidrato de bupropion, un aglutinante y un lubricante; y (ii) un recubrimiento de liberación controlada que prÆctieamente rodea dicho nücleo; donde dicha composición proporciona una liberación controlada de dicho bromhidrato de bupropion, y reduce o
30 evita las incidencias yio reduce la gravedad de las crisis convulsivas inducidas por
bupropion. Dichas composiciones opcionalmente pueden comprender uno o mÆs recubrimientos que rodean el nUcleo y/o el recubrimiento de liberación controlada tal
como un recubrimiento de barrera contra la humedad, recubrimiento entØrico o un recubrimiento que afecta la integridad fisica y/o la apariencia de la composición. El
35 aglutinante Se puede seleccionar entre los aglutinantes farmacØuticos conocidos como el
alcohol polivinilico. El lubricante tambiºn se puede seleccionar entre los lubricantes farmacØuticos conocidos como el behenato de glicerilo. El recubrimiento de liberación
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controlada puede incluir un polImero insoluble en agua, un polImero soluble en agua y opcionalmente un piastificante. El polfmero insoluble en agua se puede seleccionar entre una variedad de polImeros insolubles en agua ütiles en composiciones farmacØuticas de liberaeión extendida como la etilcelulosa. El poilmero soluble en agua se puede
5 seleccionar entre una variedad de poilmeros solubles en agua ütiles en composiciones
farmacØuticas de liberación extendida como polivinilpirrolidona. El plastificante cuando estÆ presente sepuede seleccionar entre una variedad de plastificantes conocidos como
las mezclas de polietilenglicol 4000 y sebacato de dibutilo. Ciertas realizaciones de estas composiciones incluyen composiciones que se pueden administrar una vez al dia que son
10 bioequivalentes a comprimidos de WELLBUTRINTM0 ZYBANTM/WELLBUTRINTM
SR cuando se los administra una vez al dIa a un sujeto que los necesita. Estas
composiciones pueden exhibir o no un efecto por el consumo de alimentos. MÆsaun,
ciertas realizaciones de estas composiciones pueden set resistentes a la absorción rapida
de la dosis en presenciª de altas concentraciones de alcohol (por ejemplo, 40% en peso de
15 etanol).

En otra implementación particular de ciertas realizaciones de la presente invención, la composición de bupropion comprende (i) un nücleo que contiene bromhidrato de
bupropion, un aglutinante y un lubricante; y (ii) un recubrimiento de liberación
20 controlada que prªcticamente rodea dicho nücleo; donde dicho recubrimiento de
liberación controlada incluye una dispersion acuosa de un copolimero de un ester neutro
sin ningn grupo funcional, un poliglicol con un punto de fusiOn mayor a 55°C y uno 0 mÆsexcipientes farmacØuticamente aceptabies, donde dicho recubrimiento Se deposita recubriendo dicho nücleo y se cura a una temperatura al menos igual o mayor que el
25 punto de fusion del poliglicol. La composición proporciona liberación controlada de
dicho bromhidrato de bupropion y reduce o evita incidencias de crisis convulsivas
inducidas pot bupropion. Opcionalmente, este medicamento puede comprender uno o mÆsrecubrimientos adicionales rodeando el nücleo y/o un recubrimiento de liberaciOn controlada tal como un recubrimiento de barrera contra la humedad, recubrimiento
30 entCrico, recubrimiento que excluye la absorción rÆpida dela dosis en medios especificos
como el alcohol, y/o un recubrimiento que afecta la estabilidad o la integridad fIsica del medicamento y/o su aspecto fisico.

En una implementación en particular de ciertas realizaciones de la presente invención, la
35 composición de bupropion comprende multiparticulados.

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Ciertas realizaciones de la presente invención incluyen formulaciones de comprimidos de matriz de liberación controlada.

Ciertas realizaciones de la presente invención incluyen una composiciOn de bupropion
5 que comprende un segundo fÆrmaco. El segundo fÆrmaeo(por ejemplo, otros
antidepresivos, ISRS, ansiolIticos, farmacos antipsicóticos atIpicos, medicaciones que interactan con la neurotransmisiOn de la serotonina, medicaciones que interactüan con la neurotransmisión de la norepinefrmna, medicaciones que interactüan con la
neurotransmisión de la dopamina) pueden administrarse en combinación con la sal
10 bromhidrato de bupropion objeto de la presente. El segundo fÆrrnaco puede producir un
beneficio sinØrgico on la eficacia de bupropion, asi como combinaciones de fÆrmacos no sinØrgicos. Ej emplos no limitantes del segundo fªrmaco incluyen citalopram,
escitalopram, venlafaxina, quetiapina, buspirona y sus mezclas.

15 De acuerdo con un aspecto de ciertas realizaciones de la presente invención, se
proporciona una composiciOn de liberación controlada que comprende (i) un nücleo que comprende una cantidad eficaz de un bromhidrato de bupropion, un aglutinante, un lubricante; y (ii) un recubrimiento de liberación controlada rodeando dicho nücleo; y opcionalmente (iii) una barrera contra la humedad rodeando dicho recubrimiento de
20 liberaciOn controlada o el nücleo; y; en donde la composición presenta un perfil de
disoluciOn tal que despuØs de 2 horas, se libera de aproximadamente mªs de 0% a aproximadamente 20%, incluidos todos los valores y subrangos intermedios;
preferiblemente de aproximadamente 2% a aproximadamente 18%, mªs preferiblemente
de aproximadamente 4% a aproximadamente 8%, o aproximadamente 5%, del contenido
025 de bromhidrato de bupropion; despuØs de 4 horas, se libera de aproximadamente 15% a
aproximadamente 45%, incluidos todos los valores y subrangos intermedios;
preferiblemente de aproximadamente 21% a aproximadamente 37%, mÆspreferiblemente
de aproximadamente 28% a aproximadam.ente 34%, o aproximadamente 32%, del
contenido de bronihidrato de bupropion; despuØs de 8 horas, se libera de
30 aproximadamente 40% a aproximadamente 90%, incluidos todos los valores y subrangos
intermedios, preferiblemente de aproximadamente 60% a aproximadamente 85%; mÆs preferiblemente de aproximadamente 68% a aproximadamente 74%; o aproximadamente 74%, del contenido de bromhidrato de bupropion, y despuØs de 16 horas, se libera de aproximadamente 80% a aproximadamente 100% incluidos todos los valores y subrangos
35 intermedios, preferiblemente no menos de aproximadamente 93%; mÆs preferiblemente
no menos de aproximadamente 96%, aun mÆs preferiblemente no menos de aproximadamente 99%, del contenido de bromhidrato de bupropion, cuando se usa un

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diseflo de aparato de la USP con un medio de disolución tal como se indica en la USP
(por ejemplo, un Aparato Tipo 1 de la USP a 75 rpm, 900 ml, HC1 0,1N, a 37°C + 0,5°C);
y en donde la composición de bromhidrato de bupropion es mÆsestable que otra composicion por Jo demÆs similar oidØntica que contenga una cantidad molar
5 equivalente de clorhidrato de bupropion cuando cada una se almacena en condiciones de
almacenamiento acelerado (por ejemplo, cuando se almacena durante 3 meses o 6 meses
a 40°C y COfl un 75% de humedad relativa), y reduce o evita las incidencias yio reduce la gravedad de las crisis convulsivas inducidas por bupropion.

10 En ciertas realizaciones, la composición exhibe un perfil de disolución tal que despuØs de
2 horas se libera no mÆs deaproximadamente 0% a aproximadamente 40%, incluidos
todos los valores y subrangos intermedios, del contenido de brornhidrato de bupropion, despuØs de 4 horas se libera de aproximadamente 40% a aproximadamente 75%,
incluidos todos los valores y subrangos intermedios, del contenido de brornhidrato de
15 bupropion, despuØs de 8 horas se libera no menos de aproximadamente 75% a
aproximadamente 99%, incluidos todos los valores y subrangos intermedios, del
contenido de bromhidrato de bupropion, y despuØs de 16 horas se libera no menos de aproximadamente 85% a aproximadamente 100%, incluidos todos los valores y
subrangos intermedios del contenido de bromhidrato de bupropion, cuando se usa un
20 diseiio de aparato de la USP con un medio de disolución tal como se indica en la USP
(por ejemplo, un Aparato Tipo 1 de la USP a 75 rpm, 900 ml, HC1 0,1N, a 37’C1 0,5°C).

Ciertas realizaciones de la presente invención incluyen una composición de bupropion

10 que comprende de aproximadamente 50 mg a aproximadamente 1000 mg de bromhidrato
25 de bupropion, incluidos 75 rug, 100 mg, 125 mg, 150 mg, 174 mg, 175 mg, 200 mg, 225
mg, 250 mg, 275 mg, 300 mg, 325 mg, 348 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450
mg, 475 mg, 500 mg, 510 mg, 520 mg, 522 mg, 525 mg, 530 mg, 540 mg, 550 mg, 560
mg, 570 mg, 575 mg, 580 mg, 590 mg, 600 mg, 625 mg, 650 mg, 675 mg, 700 mg, 725
mg, 750 mg, 775 mg, 800 mg, 825 mg, 850 mg, 875 mg, 900 mg, 925 mg, 950 mg, 975
30 mg y todos los valores y rangos intermedios. Por ejemplo, ciertas realizaciones incluyen
una composicion que comprende 174 mg, 348 mg o 522 mg de bromhidrato de bupropion por dosis unitaria.

De acuerdo con un aspecto de ciertas realizaciones de la presente invenciOn se
35 proporciona un comprimido de absorciOn mejorada que comprende (i) un nücleo que
comprende una cantidad eficaz de un bromhidrato de bupropion, un aglutinante, un lubricante; y (ii) un recubrimiento de liberaciOn controlada rodeando dicho nücleo; y

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donde el comprimido de absorción me] orada presenta un perfil de disolución tal que
despuØs de 2 horas, se libera de aproximadamente 0% a aproximadamente 25%, preferiblemente de aproximadamente 10% a aproximadamente 20%, incluidos todos los valores y subrangos intermedios del contenido de bromhidrato de bupropion; despuØs de
5 4 horas se libera de aproximadamente 25% a aproximadamente 55%, preferiblemente de
aproximadamente 30% a aproximadamente 50%, incluidos todos los valores y subrangos intermedios del contenido de bromhidrato de bupropion; despuØs de 8 horas se libera de aproximadamente 60% a aproximadamente 99%, preferiblemente de aproximadamente
70% a aproximadamente 90%, incluidos todos los valores y subrangos intermedios del
10 contenido de bromhidrato de bupropion, y despuØs de 16 horas se libera de
aproximadamente 70% a aproximadamente 100%, preferiblemente mÆs de aproximadamente 80%, incluidos todos los valores y subrangos intermedios, del
contenido de bromhidrato de bupropion, cuando se usa un diseflo de aparato de la USP
con un medio de disolución tal como se indica en la USP (por ejemplo, un Aparato Tipo
15 1 de la USP a 75 rpm, 900 ml, FIC1 0,1N, a 37°C 1 0,5°C); y en donde el comprimido de
absorción mejorada de bromhidrato de bupropion es mÆs estableque otra composición
por lo demÆs similar oidØntica que contenga una cantidad molar equivalente de
clorhidrato de bupropion cuando cada una Se almacena en condiciones de
almacenamiento acelerado (por ejemplo, cuando se almacena durante 3 meses 0 6 meSes
20 a 40°C y COfl un 75% de humedad relativa), y reduce o evita las incidencias y/o reduce la
gravedad de las crisis convulsivas inducidas por bupropion.

En ciertas realizaciones la composición de bromhidrato de bupropion puede comprender
un perfil de disolución tal que despuØs de 2 horas se libera de mÆsde aproximadamente
 25 0% a aproximadamente 40%, incluidos todos los valores y subrangos intermedios, del
contenido de bromhidrato de bupropion de la misma; despuØs de 4 horas se libera de aproximadamente 40% a aproximadamente 75%, incluidos todos los valores y subrangos intermedios, del contenido de bromhidrato de bupropion de la misma; despuØs de 8 horas
se libera de aproximadamente 75% a aproximadamente 99%, incluidos todos los valores
30 y subrangos intermedios, del contenido de brornhidrato de bupropion de la misma; y
despuØs de 16 horas se libera no menos de aproximadamente 85% a aproximadamente
100%, incluidos todos los valores y subrangos intermedios del contenido de bromhidrato
de bupropion de la misma, cuando se usa un diseflo de aparato de la USP con un medio
de disolución tal como se indica en la USP (por ejemplo, un Aparato Tipo 1 de la USP a
35 75 rpm, 900 ml, HCl 0,1N, a 37°C – 0,5°C).

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Segün se trata mÆs adelante, la disolución in vitro de bupropion de las formulaciones de liberación controlada o extendida de acuerdo eon ciertas realizaciones de la invención se puede determinar mediante mØtodos bien conocidos por los tØcnicos con experiencia en
ci area farmacØutica. La farmacopea de los Estados Unidos (USP) asi como sus
5 contrapartes europea y japonesa contienen mØtodos adecuados que se ejemplifican mÆs
adelante. Esto ineluye a modo de ejemplo efeetuar la disolución en un aparato 1 de la
USP (MØtodo de la cesta de tipo rotatorio) en 900 ml de agua, HC1 0,1 N, HC1 0,1 N + Cetrimida a! 0,1%, soluciOn amortiguadora de la USP de pH 1,5, soluciOn amortiguadora
de acetato de pH 6,5, solución amortiguadora de fosfato de pH 7,4 a 75 RPM a 37°C +1-
10 0,5°C o efectuar la disoiueión usando un medio de disolueión USP-3 corno LGS con un
pH de 1,2; solución amortiguadora de acetato con un pH de 4,5 o solución amortiguadora
de fosfato con un pH de 6,8.

Se conocen composiciones estabies de bromhidrato de bupropion (por ejemplo,
15 composiciones de bromhidrato de bupropion con estabilidad mejorada en comparación
con composiciones por lb demÆs sirnilaresque contienen elorhidrato de bupropion), por ejemplo, a partir de la patente de los Estados Unidos nümero 7.241.805, cuyo contenido
se incorpora a la presente a modo de referencia.

20 BREVE DESCRIPCION DE LAS FIGURAS

La Figura I es un diagrama de flujo que muestra ci proceso global de desarroilo de los comprimidos XL de bupropion HBr.
La Figura 2 es un diagrama de flujo que demuestra ci proceso de granulación de los Ocomprimidos XL y EA de bupropion HBr.
25 La Figura 3 es un diagrama de flujo que muestra ci proceso global de obtención de los
comprimidos XL de bupropion HBr.
La Figura 4 es un diagrama de flujo que muestra ci proceso global de recubrimiento de bupropion HBr XL.
La Figura 5 es un perfil de disolueión de los comprimidos de 4 kp, de 6 a 7 kp y de 9 a 10
30 kp, que compara los efectos de la dureza sobre la disolución en ci estudio sobre ci lote
BUP-HBr-XL-009-5.

La Figura 6 es un perfil de disoluciOn de los nücleos de bupropion HBr de 348 mg que se comprimieron usando punzones de 9mm en el estudio sobre ci lote BUP-HBr-XL-009-5.
La Figura 7 es un perfil de disolución de los nücieos de bupropion HBr de 348 mg que Se
35 comprimieron usando punzones de 10 mm en ci estudio sobre ci lote BUP-HBr-XL-009-

5.

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La Figura 8 es una comparación de perfiles de disolución de los nücleos de 9 mm y 10
mm de diÆmetrode 348 mg de bupropion HBr en ci estudio sobre el lote BUP-I-IBr-XL-009-5.

La Figura 9 es un perfil de disoluciOn de los de 174 mg en ci estudio sobre el lote BUP-
5 HBr-XL-021-5.

La Figura 10 es un perfil. de disoiución de BUP-HBr-XL-348 mg-013-5 (con 28 mg, 30
mg, 32 mg y 34 mg de aumento de peso).
La Figura 11 es un perfil de disolución de BUP-HBr-XL-348 mg-013-5 (con 5 mg, 6 mg
y 7 mg de aumento de peso).
10 La Figura 12 es un perfil de disolución de BUP-HBr-XL-348 mg-018-5 (con 26 mg, 28
mg, 30 mg y 32 mg de aumento de peso).
La Figura 13 es un perfil de disolución de BUP-HBr-XL-348 mg-01 8-5 (con 7 mg de aumento de peso).
La Figura 14 es un perfil de disolución de BUP-HBr-XL-174 mg-022-5 (con 22 mg, 24
15 mg, 28 mg y 30 mg de aumento de peso).
La Figura 15 es un perfil de disolución de BUP-HBr-XL- 174 mg-022-5 (con 5 mg, 6 mg
y 7 mg de aumento de peso).
La Figura 16 es un perfil de disolución de BUP-HBr-XL-348 mg-023-5 (con 26 mg, 28
mg, 30 mg y 32 mg de aumento de peso).
20 La Figura 17 es un perfil de disolución de BUP-HBr-XL-348 mg-025-5 (con 26 mg, 28
mg, 30 mg y 32 mg de aumento de peso).
La Figura 18 es un perfil de disolución de BUP-HBr-XL-348 mg-025-5 (con 5 mg, 6 mg
y 7 mg de aumento de peso).
La Figura 19 es un perfil de disolución de BUP-HBr-XL-348 mg-026-5 (con 26 mg, 28
125 mg, 30 mg y 32 mg de aumento de peso).
La Figura 20 es un perfil de disoluciOn de BUP-HBr-XL-174 mg-027-5 (con 22 mg, 24
mg y 26 mg de aumento de peso).
La Figura 21 es un perfil de disolución de BUP-HBr-XL-174 mg-027-5 (eon 4 mg, 5 mg,
6 mg y 7 mg de aumento de peso).
30 Figura 22: Actividad de crisis convulsivas en ci hipocampo durante la fase de
preadministración de 30 mg/kg de dosis de prueba.
Figura 23: Actividad de crisis convulsivas en ci hipocampo durante la fase de preadministraciOn de 60 mg/kg de dosis de prueba.
Figura 24 A y B: Actividad de crisis convulsivas en ci hipocampo durante la fase de
35 preadministración de 100 mg/kg de dosis clorhidrato de bupropion de prueba.
Figura 25 A y B: Actividad de crisis convulsivas en el hipocampo durante la fase de preadministración de 100 mg/kg de dosis bromhidrato de bupropion de prueba.

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Figura 26: Se muestra la cantidad logaritmica relativa de convulsiones, graves,
moderadas o leves, en ratas a las que se administra bromhidrato de bupropion o
clorhidrato de bupropion.
Las Figuras 27-32 muestran perfiles de disolución comparativos de comprimidos de
5 Bupropion HBr XL en distintos medios.
Figura 33: Representación grÆficade la concentración de bupropion en plasma media con respecto al tiempo para ci Estudio B06-756PK-10121 (3230)
Figura 34: Representación grÆficade la concentración de hidroxibupropion en plasma
media con respecto al tiempo para ci Estudio B06-756PK-10121 (3230)
10 Figura 35: Representación grÆficade la concentración de treoamino alcohol de bupropion
en plasma media con respecto al tiempo para el Estudio B06-756PK-10121 (3230)
Figura 36: Representación grÆficade la concentración de eritroamino alcohol de
bupropion en plasma media con respecto al tiempo para ci Estudio B06-756PK-10121
(3230)
15 Figura 37: Representación grÆfica de compuesto ponderado con actividadfarmacologica
(PAWC) en plasma medio con respecto al tiempo para el Estudio B06-756PK-10121
(3230)
Figura 38: Representación grÆficade la concentración de bupropion en plasma media con respecto al tiempo para ci Estudio B06-755PK-10121 (3228)
20 Figura 39: Representación grÆficade la concentración de bupropion en plasma media con
respecto al tiempo para ci Estudio B06-755PK-10121 (3228) - Ampliado mostrando
solamente puntos de datos de 0 - 36 horas
Figura 40: RepresentaciOn grÆfica de laconcentración de hidroxibupropion en plasma

0 media con respecto al tiempo para el Estudio B06-755PK-10121 (3228)
25 Figura 41: Representación grÆficade la concentración de treoamino alcohol de bupropion
en plasma media con respecto al tiempo para ci Estudio B06-755PK-10121 (3228)
Figura 42: Representación grÆfica dela concentración de eritroamino alcohol de
bupropion en plasma media con respecto al tiempo para ci Estudio B06-755PK-10121
(3228)
30 Figura 43: RepresentaciOn grÆficade compuesto ponderado con actividad farrnacológica
(PAWC) en plasma rnedio con respecto al tiempo para el Estudio B06-755PK-10121
(3228)
Figura 44: Representación grÆfica dela concentración de bupropion en plasma media con respecto al tiempo para el Estudio B06-754PK-10 121 (3229)
35 Figura 45: Representación grªfica de la concentración de bupropion en plasma media con
respecto al tiempo para el Estudio B06-754PK-10121 (3229) - Ampliado mostrando solamente puntos de datos de 0 - 36 horas

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Figura 46: Representación grÆficade la concentración de hidroxibupropion on plasma
media con respecto al tiempo para el Estudio B06-754PK-10121 (3229)
Figura 47: Representación grÆfica de la concentración de treoamino alcohol de bupropion
en plasma media con respecto al tiempo para el Estudio B06-754PK-10121 (3229)
5 Figura 48: RepresentaciOn grÆfica dela concentración de eritroamino alcohol de
bupropion en plasma media con respecto al tiempo para el Estudio B06-754PK-10 121
(3229)
Figura 49: RepresentaciÆn grÆficade compuesto ponderado con actividad farmacológica (PAWC) en plasma medio con respecto al tiempo para el Estudio B06-754PK-10 121
10 (3229)
Figura 50: Representación grÆfica de la concentración de bupropion en plasma media con respecto al tiempo para el Estudio B06-802PK-10121 (AA40055)
Figura 51: RepresentaciOn grÆfica de laconcentración de hidroxibupropion en plasma
media con respecto al tiempo para el Estudio B06-802PK-10121 (AA40055)
15 Figura 52: Representación grÆfica de la coneentración de treoamino alcohol de bupropion
en plasma media con respecto al tiempo para el Estudio B06-802PK-10121 (AA40055) Figura 53: Representación grªfica de la concentración de eritroamino alcohol de
bupropion en plasma media con respecto al tiempo
Figura 54: Representación grÆficade compuesto ponderado con actividad farmacológica
20 (PAWC) on plasma medio con respecto al tiempo

DEFINICIONES

Las siguientes definiciones se proporcionan con el objetivo de describir mÆs especificamente la invención. Por lo demÆs, debe asignarse atodos los tØrminos su
 25 significado comim tal como serlan interpretados por los expertos en la tØcnica, es decir,
on las formulaciones farmacØuticas de fÆrmacos.

El tØrmino "crisis convulsiva", como se usa aqul, significa un fenómeno
electrofisiológico anormal (por ejemplo, actividad elØctrica involuntaria) del cerebro, lo
30 que resulta en una sincronización anormal de la actividad neuronal elØctrica quo puede
resultar en una amplia variedad de manifestaciones, de las cuales los ejemplos no
limitantes incluyen movimientos tónicos o clónicos, convulsiones, mirada perdida, mordedura de la lengua, micción, pØrdida de conciencia, alteración del estado mental, sIntomas psIquicos tales como dØjà vu o jamais vu y combinaciones de los mimos.
35 Ejemplos no limitantes de tipos de crisis convulsivas incluyen: (i) crisis convulsivas
parciales (por ejemplo, crisis convulsivas focales) tales como crisis convulsivas parciales simples, crisis convulsivas parciales complejas (por ejemplo, crisis convulsivas del lóbulo

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temporal o psicornotoras) y crisis convulsivas parciales que devienen en crisis convulsivas secundariamente generalizadas; (ii) crisis convulsivas generalizadas tales
como crisis convulsivas de ausencia (por ejemplo, crisis convulsivas del pequeæo mal),
crisis convulsivas mioclónicas, crisis convulsivas clónicas, crisis convulsivas tOnicas,
5 crisis convulsivas tOnicoclOnicas (por ejemplo, crisis convulsivas del gran ma!) y crisis
convulsivas atónicas; y (iii) crisis convulsivas epilØpticas sin clasificar.

Las expresiones "crisis convulsivas inducidas por bupropion" o "crisis convulsivas
asociadas a la adrninistración de bupropion", como se usan en la presente, se usan
10 indistintamente y significan crisis convulsivas que resultan de la administración de
bupropion o una mezcla de bupropion con uno o mÆsfÆrmacos diferentes.

La expresión "incidencias de crisis convulsivas inducidas por bupropion", como se usa on
la presente en referencia a la administración de bupropion, se define con el significado de
15 cantidad de crisis convulsivas inducidas por bupropion segün se detennina mediante
observaciones del comportamiento de convulsiones u otros movirnientos caracteristicos
de una crisis convulsiva; y/o segilin se determina mediante observaciones en electroencefalograma ("EEG") de la actividad elØctrica del cerebro caracteristica de una
crisis convulsjva usando electrodos de superficie colocados a nivel cortical y/o electrodos
20 de profundidad implantados en el hipocampo.

La expresión "reducir incidencias de crisis convulsivas inducidas por bupropion", como
se utiliza en la presente on referencia a la administración de bupropion, Se define con el significado de la administraciOn de bromhidrato de bupropion o composiciones que
25 contienen brornhidrato de bupropion resulta on menos incidencias de crisis convulsivas
inducidas por bupropion en cornparación con la administración de de una cantidad molar equivalente de clorhidrato de bupropion o una com.posición de otro modo idØntica que contiene una cantidad molar equivalente de clorbidrato de bupropion, cuando se expone a condiciones idØnticas y luego de perfodos de tiempo idØnticos.

30

Las expresiones uefectos adversos asociados al bupropion o "efectos secundarios del bupropion", como se usan aqui, se usan indistintamente y significan reacciones al fÆrmacoadversas que resultan de la administración de bupropion o una mezcla de
bupropion con uno o mÆsfÆrmacosdistintos, ejemplos no lirnitantes de los cuales
35 incluyen crisis convulsivas, nÆuseas,vómitos, excitaciOn, agitaciOn, visiOn borrosa,
inquietud, temblores posturales, alucinaciones/estados de confusiOn con el potencial de abuso, ansiedad, insomnio, dolores de cabeza y/o migrafias, sequedad en la boca,

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constipaciOn, temblores, trastornos del suefio, problemas dennatológicos (por ejemplo, sarpullidos), signos y sIntomas neuropsiquiªtricos (por ejemplo, ideas delirantes y
paranoia), aumento de peso y combinaciones de los mismos.

5 El tØrmino "depresiOn", como se usa aqul, Se refiere a cualquier trastorno del sistema
nervioso y/o trastorno mental. Ejemplos no limitantes de "depresión" incluyen trastorno depresivo mayor, trastorno del humor con depresión bipolar, trastorno de adaptación del humor y trastorno del humor posparto.

10 El tØrmino "condición", como Se usa aqul en referencia a la administración de bupropion,
significa una afección, enfermedad o trastorno que puede tratarse con bupropion.
Ejemplos no limitantes de los mismos incluyen depresión, trastorno afectivo estacional, trastornos de ansiedad, trastorno de ansiedad generalizado, trastorno de ansiedad social, trastorno obsesivo compulsivo, trastorno de estrØs postraumÆtico (TEPT), trastornode
15 panico, trastornos que requieren un efecto estimulante, trastorno de hiperactividad por
deficit atencional (THDA), narcolepsia, hipersomnia, trastornos de abuso de fÆrrnacos, dependencia de estimulantes, dependencia de marihuana, dependencia de nicotina,
obesidad, disfunción sexual femenina y masculina (por ejemplo eyaculaciOn precoz),
sIndrome premenstrual, trastorno disfórico premenstrual, dolor neuropÆtico, fibromialgia,
20 neuropatIa diabCtica, infecciOn viral, apnea del sueæo, trastornos del sue-no, migraflas,
enfermedad de Parkinson, sIndrome de las piernas inquietas y combinaciones de los

mismos.

Los tØrminos "tratamiento" o "tratar", como se usan aqul en referencia a una afección, y
025 como Se entienden en la tØcnica, se definen con el significado de un abordaje para
obtener resultados beneficiosos o deseados, ineluidos resultados cilnicos. "Tratamientot’ tambiØn puede significar prolongar la supervivencia de un sujeto en comparación con la supervivencia esperada del sujeto si no se recibe tratamiento,

30 Las expresiones "con riesgo", "paciente en riesgo" y "un sujeto con riesgo de crisis
convulsivas inducidas por bupropion" se refieren a aqueflos sujetos que se sabe, a travØs
de una enfermedad existente, una enfermedad anterior, antecedentes de crisis
convulsivas, anterior exposiciOn, prueba, dosificaciOn u otra administración de
clorhidrato de bupropion, que tienen una propensión mayor a sufrir crisis convulsivas
35 inducidas por bupropion en comparación con un sujeto que no exhibe crisis convulsivas
en condiciones iguales o similares y/o un sujeto que, en base a una evaluación clfnica de

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su salud, otros medicamentos y/o tratamientos, se espera que tenga una propensión mayor a tener actividad de crisis convulsivas inducidas por bupropion.

El tØrmino "paliar", como se usa aqul en referencia a una afección, significa que ci grado
y/o las manifestaciones cilnicas indeseables de una afección o enfermedad Se reducen yb
ci tiempo que lieva el empeoramiento de la enfermedad se ralentiza o se alarga en comparación con la afección sin tratar.

La expresión "cantidad efectiva" o "cantidad farmacØuticamente efectiva", como se usan
10 aqul, se usan indistintamente, y se definen con ci significado de cantidad de fÆrmaco
activo (por ejemplo, bromhidrato de bupropion) o polimorfo o enantiómero del mismo,
que es suficiente para producir una respuesta bioiogica apreciable cuando se administra a
un paciente. Se apreciarÆ que la dosis terapØutica precisa dependerÆ de la edady ci
estado del paciente y la naturaleza de la afecciOn a ser tratada y serÆ en ültimo tØrmino a
15 juicio del medico tratante.

Las expresiones "estabilidad mejorada", "mayor estabilidad", "estabilidad aumentada" o "mÆs estable" como seusan aqul en referencia al bromhidrato de bupropion, pueden
usarse indistintainente en esta solicitud, y se definen con ci significado de que ci
20 bromhidrato de bupropion, o una composición que contiene bromhidrato de bupropion,
muestra menos degradacion segün se determina por la formaciOn de menos de al menos
un producto de degradacion caracteristico de la degradacion de bupropion, que una
cantidad molar equivalente de clorhidrato de bupropion o una composición por lo demÆs similar o idØntica de clorhidrato de bupropion, cuando se expone a condiciones similares
25 o idØnticas. Ejempios no limitantes de afecciones son las descritas, por ejemplo, en la
patente de los Estados Unidos nümero 7.241.805.

La expresión "menos degradaciOn", como se usa aquI en referencia a bromhidrato de bupropion o a una composiciOn que contiene bromhidrato de bupropion, se define con ci
30 significado de cualquier disminuciOn cuantificable en la cantidad de al menos una
impureza de degradacion de bupropion caracterIstica de la degradacion de bupropion, y/o cualquier diferencia cuantificable en la retención de la potencia, con relación a una
cantidad molar equivalente de clorhidrato de bupropion o una composición por lo demªs similar o idØntica que contiene una cantidad molar equivalente de clorhidrato de
35 bupropion, cuando se expone a condiciones similares o idCnticas.
Las expresiones "producto de degradación", "producto de dcgradación de bupropion", "impureza de degradacion de bupropion" o "impureza", como se usan aqul con referencia

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a la degradación de bupropion, se usan indistintamente y se definen de modo de incluir
los enumerados en la pÆgina281 de la 26’ edición de la USP y todos los otros productos
de degradación que puedan aparecer como picos en un cromatograma durante ci ensayo
que son caracterfsticos de la degradacion del bupropion.
5

Las expresiones "perfil de disolución" o "perfil de liberación", como se usan aqul, se
usan indistintamente en esta solicitud y se definen con el significado de una prueba de control de calidad lievada a cabo de acuerdo con las instrucciones que se encuentran en la Farmacopea de los Estados Unidos ("USP"), es decir, utilizando an diseflo de aparato de
10 la USP con un medio de disolución tal como se indica en la USP. Las pruebas de
disolución in vitro miden la velocidad y el alcance de la disolución del fÆrmaco activo en
un medio de disolución acuoso. La velocidad de disolución o velocidades de liberación
in vitro de las formas farmacØuticas de liberación modificada de la presente invenciOn pueden medirse utilizando uno de los muchos disefios de aparatos de la USP y medios de
15 disolución, ejemplos no limitantes de los cuales incluyen un diseflo de aparato Tipo 1 de
a USP o un aparato Tipo 2 de la USP, con un medio de disolución seleccionado de agua;
HC1 0,1N; HC1 0,1N con cloruro de sodio agregado (por ejemplo, 15,7g NaC1/litro); HC1 0,1N con cetrimida al 0,1% agregada; solución amortiguadora de la USP de pH 1,5;
solución amortiguadora de acetato de pH 4,5; solución amortiguadora de fosfato de pH
20 6,5; solución amortiguadora de fosfato de pH 6,8 y solución amortiguadora de fosfato de
pH 7,4.

La expresión "absorción rÆpida de la dosis", como Se usa aqul con respecto a la
"absorciOn rÆpida de la dosis inducidapor alcohol", se define con ci significado de la
025 liberación prematura no planeada (in vitro) de al menos un fÆrmacode una forma
farmacØutica de liberación modificada. La expresión "liberación prematura", como se usa
aquf, se define con ci significado de una liberación de al menos un fÆrrnaco deuna forma farmacØutica de liberaciOn modificada en medios de disolución que contienen alcohol
(por ejemplo, un medio de disolución que contiene de aproximadamente 5% a
30 aproximadamente 40% de etanol), en donde la velocidad de liberación es mÆs rÆpidaque
la velocidad de liberación del o de los fÆnnacos idØnticos de la formafarmacØutica de iiberación modificada idØntica en los medios de disolución por lo demÆs idØnticosque no contienen alcohol (por ejemplo, un medio de disolución que contiene aproximadamente
HCl 0,1 N a! 100%).
35 Las expresiones "resistente a! alcohol", "resistente a! etanol", "resistente a la absorción
rÆpidade la dosis", "resistente a la absorciOn rÆpidade Ia dosis inducida por alcohol" y
"que resiste la absorciOn rÆpida dela dosis", como se usan aqu!, se usan indistintamente y

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se definen con ci significado de la capacidad de la forma farmacØutica de modificar la liberaciOn (in vitro) de at menos un fÆrmaco en presencia dealcohol (por ejemplo, de aproximadamente 5% a aproximadamente 40% de etanol), de forma tal que no haya una liberación prernatura de at menos una forma de fÆrrnaco de la forma farrnacØuticade
5 liberación modificada. Por ejemplo, en ciertas realizaciones, la velocidad de liberación
de al menos un fÆrmaco de unaforma farmacØutica de liberación modificada en medios
de disoiuciOn que contienen alcohol (por ejemplo, un medio de disolución que contiene
de aproximadamente 5% a aproximadamente 40% de etanol) es mÆs lenta que la
velocidad de ljberación del o de los fÆrmacos idØnticos dela forma farmacºutica de
10 iiberaciOn modificada idØntica en medios de disolueión que no contienen alcohol (por
ejemplo, un medio de disolución que contiene aproximadamente HC1 0,1 N at 100%).

Las expresiones "otro fÆrrnaco" o "segundofÆrmaco",como, se usan aqul, significan un fÆrmaco diferentede bupropion, incluidos pero no exciusivamente, antidepresivos, otros
15 fÆrmacos neurosiquiÆtricos, antipsicóticosatIpicos, fÆrmaco que afectala
neurotransmisión central o perifØrica de la serotonina, fÆrrnacosque afectan la neurotransmisión central de norepinefrina, fªrmacos que afeetan la neurotransmisión
central de dopamina, vasodilatadores, ansiolIticos, moduladores del apetito, fÆrmacos moduladores del sueæo,ISRS, antivirales, analgØsicos, antirnigraæosos, antiinflamatorios
20 (tanto esteroideos como no esteroideos), agonistas del receptor de serotonina y mÆs
particularmente pueden incluir citalopram, escitalopram, venlafaxina, clozapina,
melperona, amperozida, iloperidona, risperidona, quetiapina, olanzapina, ziprasidona, aripiprazol, reboxetina, Viagrafi, sertralina, paroxetina, fluoxetina, gabapentina, Æcido vaiproico, arnitriptilina, lofepramina, fluvoxamina, imipramina, mirtazapina, nefazodona,
25 nortriptilina, SAM-E, buspirona, combinaciones de Østos y sus sales farmacØuticamente
aceptables (por ejemplo, las sales de clorhidrato, las sales de bromhidrato, las sales de yodhidrato y las sales de sacarinato), asi como las formas anhidras, hidratadas y
solvatadas, polimorfos, profÆrrnacosy los enantiOmeros individual y ópticamente activos

del fÆrmaco.
30

La expresión "forma farmacØutica", como se usa aqul, se define con el significado de una preparación o sisterna farmacØuticos en los que se incluye una dosis de at menos un fÆrmacoactivo. Por ejemplo, una forma farmacØutica puede incluir al menos una forma farrnacØutica de liberación modificada, at menos una forma farrnacØutica osmOtica, at
35 menos una forma farrnacØutica de liberaciOn modificada por erosiOn, ci menos una forma
farmacØutiea de liberación modificada por disoluciOn, at menos una forma farmacØutica
de liberación modificada por difusión, at menos un ni.kleo de la matriz de liberación

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modificada, at menos un recubrimiento del nüeleo de la matriz de liberación modificada,
at menos una forma farxnacØutica con recubrimiento entØrico, at menos una forma farmacØutica rodeada por at menos un subrecubrimiento osmótico, cÆpsulas, minicomprimidos, comprimidos oblongos, microparticulas sin recubrir, micropartleulas
5 recubiertas con al menos un recubrimiento de liberación modificada o cualquier
combinaciOn de los mismos.

El tØrmino "medicamento", como se usa aquf, se refiere a formas farmacØuticas posibles orales y no orales, incluidas pero no exclusivamente, todas las formas farmacØuticas de
10 liberaciOn modificada, los sistemas de liberaciOn controlada por osmosis, los sistemas de
liberación controlada pot erosion, los sistemas de liberación controlada por disolución,
los sistemas de liberación controlada por difusión, los comprimidos de matriz, los comprimidos con recubrimiento entØrico, los comprimidos con recubrimiento simple y doble (incluidos los comprimidos de liberación extendida y de absorciOn mejorada
15 descritos aquf), las cÆpsulas, los minicomprimidos, loscomprimidos oblongos, las perJas
recubiertas, los grÆnulos,los esferoides, los pelets (granulos comprimidos), las micropartIculas, las suspensiones, las tópicas como las composiciones transdØrmicas y transmueosas y los sistemas de administración (que contienen o no matrices),
composiciones inyectables e inhalables.
20

"Formas farmacØuticas de liberación modificada", como se usa aquf, se define (por
ejemplo como en la Farmacopea de los Estados Unidos, o "USP") como aquellas cuyas caracteristicas de liberación del fÆrmaco en el transcurso del tiempo y/o la ubicación se
eligen de modo de conseguir objetivos terapØuticos o de conveniencia que no son
1025 ofrecidos por las formas farmacØutieas de liberación inmediata convencionales. La
velocidad de liberación del fÆrmaco activo de una formafarmacØutiea de liberación
modificada es controlada por caracterIsticas de la forma farmacØutica y/o en combinaeiOn
con condiciones fisiolOgicas o ambientales en vez de solamente pot las condiciones
fisiológicas o ambientales. Las formas farmacØuticas de liberaciOn modificada de ciertas
30 realizaciones pueden ser contrastadas con las formas farmacØuticas de liberaciOn
inrnediata que producen de manera caracteristica grandes relaciones de concentraciOn maxima/minima plasmÆtica de fÆrmaco(CmÆxlCmin)debidas a la absorción rªpida del fÆrmaco enel organismo (es decir, in vivo, en relación con el Indice terapØutico del fÆrmaco;es decir, la relación de la concentraciOn maxima de fÆrmaco necesariapara
35 producir y mantener una respuesta farmacolOgica deseable). En las formas farmacØuticas
de liberaciOn imnediata convencionales, el contenido del fÆrmaco selibera en el tubo digestivo en un perIodo corto, y los niveles plasmÆticos delfÆrmaco alcanzanel mÆximo
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poco despuØs de la dosificación. El disefio de las formas farmacØuticas de liberación inmediata convencionales se basa en general en conseguir la mayor velocidad de
liberación posible del fÆrmaco,y por consiguiente su absorción, a menudo a riesgo de
crear efectos colaterales indeseables relacionados con la dosis. Por otra parte, las formas
5 farmacØuticas de liberación modificada de ciertas realizaciones de la invención, mejoran
el valor terapØutico del fÆrmaco activo al reducir la relación entre la concentración maxima/minima de fªrmaco en el plasma (Cmªx/Cmin) mientras mantienen los niveles plasrnÆtieos delfÆrrnacodentro de la ventana terapØutica. Las formas farrnacØuticas de liberaciOn modificada de ciertas realizaciones de la invención intentan administrar

10 cantidades terapØuticamente eficaces de brornhidrato de bupropion y mezclas de
brornhidrato de bupropion con al menos otro fÆrmaco como unadosis una vez al dia para
que la relación Cm.ÆxlCmIn enel plasma en el estado estacionario sea menor que el
Indice terapØutico y para mantener los niveles de fÆrmaco a niveles eficaces constantes
para proporcionar un beneficio terapØutico durante un perlodo de tiempo (por ejemplo, un
15 periodo de 24 horas). Por consiguiente, las formas farmacØuticas de liberación
modificada de ciertas realizaciones de la invención evitan grandes fluctuaciones entre las concentraciones maxima y minima que se yen norinalmente con las formas farmacØuticas
de liberación inmediata o convencionales y pueden proporcionar una curva de
concentración sØrica sustancialmente plana a lo largo de todo el perlodo terapØutico. Las
20 formas farmacØuticas de liberación modificada se pueden diseæar paraproporcionar un
aumento rÆpido de laconcentración plasmÆtica de la sal de bupropion que permanece sustancialmente constante dentro del intervalo terapØutico de la sal de bupropion durante
un perlodo de tiempo (por ejemplo, un perlodo de 24 horas). Como alternativa, las
formas farmacØuticas de liberaciOn modificada se pueden disenar para proporcionar un
25 aumento rÆpido dela concentración plasmÆticadel fÆrniaco, lacual, aunque puede no
permanecer constante, disrninuye a una velocidad tal que la concentración plasrnÆtica permanece dentro del intervalo terapØutico durante un perlodo (por ejemplo, un perlodo
de 24 horas). Las formas farmacØuticas de liberación modificada de ciertas realizaciones
de la invención pueden construirse de muchas formas conocidas por los tØcnicos con
30 experiencia en las tØenicas de administraciOn de fªrmacos y como se describe en la
tØcnica anterior. La USP considera que las expresiones liberación controlada, liberación prolongada y liberaciOn sostenida son intercambiables. En consecuencia, las expresiones "liberación modificada", "liberación controlada", "control de la liberación", "liberación controlada por velocidad", "liberación extendida", "liberación prolongada" y "liberación
35 sostenida" se usan indistintamente aquf. A los efectos de esta descripción, la definición de
la expresión "liberación modificada" abarca el alcance de las definiciones.para las

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expresiones "liberación extendida", "absorción mejorada", "liberación controlada",
"liberación sostenida" y "liberación retardada".

"Formas farmacØuticas de liberación controlada", "formas farmacØuticas de control de la
5 liberaeión", "formas farmacØuticas de liberación controlada por velocidad" o formas
farxnacØuticas que presentan una "liberación controlada" del bromhidrato de bupropion o mezelas de bromhidrato de bupropion y.un segundo fÆrmaco,se usan indistintamente en
esta solicitud y Se definen con el significado de formas farmacØuticas que liberan el bromhidrato de bupropion de forma controlada por unidad de tiempo in vivo. Por
10 ejemplo, pueden administrarse formas farmacØuticas de liberación controlada una vez al
dIa y liberar el bromhidrato de bupropion a una velocidad controlada y proporcionar concentraciones piasmÆticas del fÆrmacoque permanecen controladas en el tiempo dentro
del rango terapØutico del bupropion durante un perlodo de 24 horas. La velocidad de liberaciOn del bromhidrato de bupropion de una forma farmacØutica de
15 controlada es controlada por caracterIsticas de la forma farrnacØutica y/o en combinación
con condiciones fisiológicas o ambientales en vez de solamente por las condiciones fisiológieas o ambientales. Las formas farmacØuticas de liberación controlada de ciertas realizaciones de la invención pueden ser contrastadas con formas farmacØuticas de
liberación inmediata que producen de manera earacterfstica grandes relaciones de
20 concentración mÆxima’minima plasmÆtica de fÆrmaeo (CmÆx/Cmfn) debidasa la
absorción rÆpida del fÆrmacoen el organisrno (es decir, in vivo, en relación con el mndice terapØutico del fÆnnacô, es decir, la relación de la concentraciOn maxima de fÆrmaco
necesaria para producir y mantener una respuesta farmacológica deseable). En las formas farmacØuticas de liberación inmediata, el contenido de fÆrmacose libera en el tubo
1025 digestivo en un perlodo corto, y los niveles plasmÆticos de fÆrmaco alcanzanel mÆximo
poco despuØs de la dosificación. El diseflo de las formas farmacØuticas de liberaciOn
inmediata se basa en general en conseguir la mayor velocidad de liberación posible del fÆrmaco,y por consiguiente su absorción, a menudo a riesgo de crear efectos colaterales indeseables relacionados con la dosis. Por otra parte, las formas farmacºuticas de
30 liberación controlada de ciertas realizaciones de la invención, mejoran el valor
terapØutico del fÆrmaco activo al reducirla relación entre la concentraciOn
mªximalmInima de fÆrmaco en el plasma (CmÆx/CmIn) mientras mantienen losniveles piasmâticos del fÆrmaco dentrode la ventana terapØutica. Las formas farmacØnticas de liberación controlada de ciertas realizaciones de la inveución intentan administrar
35 cantidades terapØuticarnente eficaces de bromhidrato de bupropion y/o mezclas de
bromhidrato de bupropion con al menos otro fÆrmacocomo una dosis administrada al menos una vez al dIa para que la relación CmÆx!Cmfn en elplasma en el estado
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estacionario sea menor que el Indice terapØutico y para mantener los niveles de fÆrmaco a niveles eficaces constantes para proporcionar un beneficio terapºutico durante un periodo
de tiempo (por ejemplo, un perlodo de 24 horas). Por consiguiente, las formas
farmacØuticas de liberación controlada de ciertas realizaciones de la invención evitan

5 grandes fluctuaciones entre las concentraciones maxima y minima que se yen
normalmente con las formas farmacØuticas de liberación inmediata y proporcionan una
curva de concentraciön sØrica sustancialmente plana a lo largo de todo ci perfodo
terapØutico. Las formas fannacØuticas de liberación controlada de ciertas realizaciones
de la invenciÆn pueden construirse de muchas formas conocidas por los expertosen las
10 tØcnicas de la administraciOn de fÆrmacos o comose describe en la tØcnica anterior, como
por ejemplo, en formas farmacØuticas osmóticas, formas farmacØuticas multiparticuladas
y formas farm.acØuticas de retención gÆstrica.

"Formas farmac&iticas de liberación sostenida" o formas farmacØuticas que presentan
15 "liberación sostenida" del bromhidrato de bupropion o mezclas de bromhidrato de
bupropion y un segundo fÆmiaco,como Se usan aqul, se definen con ci significado de
formas farmacØuticas que se administran al menos una vez al dIa que proporcionan una liberación suficiente del bromhidrato de bupropion para proporcionar una dosis
terapØutiea poco despuØs de la administración y despuØs una liberaciOn gradual durante
20 un perlodo tal que la forma farmacØutica de liberación sostenida proporcione un beneficio
terapØutico durante un perfodo de tiempo (por ej emplo, un perlodo de 12 o 24 horas).

"Formas farrnacØuticas de liberación extendida" o formas farmacØuticas que presentan
una "liberación extendida" del bromhidrato de bupropion o mezclas del bromhidrato de
25 bupropion con un segundo fÆrmaco, comose usan aquf, Se definen con ci significado de
formas farrnacØuticas administradas al menos una vez al dia que liberan el bromhidrato
de bupropion lentarnente; de modo que las concentraciones plasrnÆticasdel bromhidrato
de bupropion se mantienen a un nivel terapØutico durante un perlodo prolongado de
tiempo tal que la forma farmacØutica de liberación extendida proporciona un beneficio
30 terapºutico durante un perlodo de tiempo (por ej emplo, un periodo de 12 o 24 horas).

"Formas farmacØutieas de liberación retardada" o formas farmacØuticas quo presentan "liberación retardada" de brornhidrato de bupropion o mezclas del bromhidrato de bupropion con un segundo fÆrmaco,como se usan aqul, se definen con ci significado de
35 formas farmacØuticas que se administran al menos una vez al dia que no liberan
eficazmente ci fÆrxnacoimnediatarnente despuØs de la administración sino
posteriormente. Las formas farmacØuticas de liberación retardada proporcionan una

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demora en el tiempo antes del eomienzo de la absorciOn del fdrmaco. Esta demora en el tiempo se denomina "tiempo de retraso (lag time)" y no se debe confundir con el "tiempo de inicio" que representa la latencia, o sea, el tiempo necesario para que el fÆrmaco
alcance la concentración eficaz minima.

"Formas farmacØuticas de absorción mejorada" o formas farmacØuticas que presentan una "absorción mejorada" del fÆrtnaco activo, como se usan aqul, se definen con el
significado de formas farmacØuticas que cuando se exponen a condiciones similares, mostrarÆn una liberación mayor y/o mÆs absorción de la base de bupropion en
10 comparación con otras formas farmacØuticas con la misma cantidad o mayor cantidad de
base de bupropion. Se puede lograr el mismo efecto terapØutico con menos base de bupropion en la forma farmacØutica de absorción mejorada en comparación con otras
formas farmacØuticas.

15 El tØrmino "micropartfcula", como se usa aquI, se refiere a una formulaciOn de un
fÆrmacoen forma de particulado discreto y es intercambiable con los tØrminos "microesferas", "particulas esfØricas", "microcÆpsulas", "particulas", "multiparticulados" "grÆnulos", "esferoides", "perlas" y "pelets".

20 El tØrmino "comprimido", como se usa aqul, se refiere a una ünica forma farmacØutica, es
decir la ünica entidad que contiene el principio farmacØutico activo que se administra al
sujeto. El tØrmino "comprimido" tambiØn incluye un comprimido que puede ser la
combinación de uno o mÆs "minicomprimidos".

1025 La expresión "matriz de liberación controlada", como se usa aqul, se define con el
significado de una forma farmacØutica en la que el bromhidrato de bupropion o mezclas
del bromhidrato de bupropion con un segundo fÆrmaco se dispersan dentrode una matriz
que puede ser soluble, insoluble o una combinación de los mismos. Las formas
farmacØuticas de matriz de liberación controlada del tipo insoluble tambiØn se denominan
30 "matrices polimØricas insolubles", "matrices hinchables" o "matrices lipIdicas" segün los
componentes que constituyen la matriz. Las formas farinacØuticas de matriz de
liberación controlada del tipo soluble tambiØn se denominan "matrices coloidales
hidrOfilas", "matrices erosionables" o "sistemas de reservorio". Las formas farmacØuticas
de matriz de liberaeiOn controlada de la invención se refieren a las formas farmacØuticas
35 que comprenden una matriz insoluble, una matriz soluble o una combinación de matrices
insolubles y solubles en las cuales la velocidad de liberaciOn es mÆs lentaque la de las
formas farmacØutieas sin matriz, sin recubrir, convencionales o de liberaciOn inmediata o

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las formas farmacØuticas de "matriz de liberación normal" sin recubrir. Las formas farmacØuticas de matriz de iiberaciOn controlada se pueden recubrir con un "recubrimiento de control de la iiberación" Para ralentizar aün mÆs la liberación de la sal
de bupropion de la forma farmacØutica de matriz de liberación controlada. Dichas formas farmacØuticas de matriz de liberación controlada, recubiertas, pueden presentar
"liberación modificada’.’, "liberación controlada", "liberación sostenida", "liberación extendida’, "liberación prolongada", "liberación retardada" o combinaciones de Østas del fÆrmaco activo.

10 La expresión "matriz de liberación normal", como se usa aquf, se define con ci
significado de formas farmacØuticas en las que el bromhidrato de bupropion o mezclas
del bromhidrato de bupropion con tin segundo f’Ærmaco se dispersan dentro deuna matriz,
que puede ser soluble o insoluble, o combinaciones de Østas Pero elaboradas de tal
manera que la liberación del fªrmaco activo imita la velocidad de liberaciOn de una forma
15 famrncØutica convencional sin matriz, sin recubrir, o de liberación inmediata que
comprende el fÆrmaco; La velocidad deliberación de las formas fannacØuticas de matriz
de liberación normal se puede ralentizar o modificar conjuntamente con tin recubrimiento
de liberación controlada.

20 Las expresiones "forma farmacØutica osmótica", "dispositivo de administración
osmótica", "forma farmacØutica osmótica de liberación modificada" o "forma
farmacØutica osmótica de liberación controlada" como se usan aqul, se usan
indistintamente en esta solicitud, y se definen con ci significado de formas farmacØuticas
que dispensan el bromhidrato de bupropion o mezclas del bromhidrato de bupropion con
025 un segundo fÆrmaco, totalmenteo en parte como resultado de la presencia de un agente
osmótico en la forma farmacØutica que conduce ci disolvente (ior ejemplo, agua, medios
de disolución, fluido gÆstrico, fluido intestinal omezclas de los mismos) hacia ci nücleo
de la forma farmacØutica, lo que facilita posteriormente la liberación del fÆrmacodesde ci
nücleo.
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Las expresiones "agente osmótico", "osmoagente", "soluto osmóticamente eficaz", "potenciador osmótico", "compuestos osmOticamente eficaces", "solutos osmóticos", "osmopolimero" y "agentes que embeben liquido osmótico", como se usan aqul, se usan indistintamente y definen eualquier material que es soluble (es decir, que puede estar total
35 o parcialmente solubilizado) o hinchabie en tin disolvente (por ejemplo, agua) que entra
en la composición y presenta tin gradiente de presiOn osmOtica a travØs de la membrana

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selectivamente permeable (por ejemplo, recubrimiento de liberación controlada), aumentando asI la presión hidrostªtica dentro de la forma farmacØntica osmótica.

Las expresiones "recubrimiento de Iiberación controlada", "recubrimiento de control de
5 la liberación", "recubrimiento de liberación modificada" y "recubrimiento de control de
la velocidad", como se usan aquI, se usan indistintamente en esta solicitud, y se definen
con el significado de un recubrimiento funcional que comprende al menos un polimero de liberación modificada. Ejemplos no limitantes de polimeros incluyen polimeros independientes del pH, polimeros dependientes del pH (como por ejemplo los tipos
10 entØricos o entØricos inversos), polimeros solubles, polimeros insolubles, ilpidos,
materiales lipIdicos o sus combinaciones. Cuando se aplica a una forma farmacØutica, ci recubrimiento de liberación controlada puede modificar (por ejemplo, ralentizar) la velocidad de liberación del fÆrmaco activo. Por ejemplo, el recubrimiento de liberaciOn controlada puede disefiarse de forma tal que cuando el recubrimiento se aplica a una
15 forma farmacØutica, Østa, conjuntamente con el recubrimiento de liberación controlada,
presenta un perfil de "libración modificada", "liberación controlada", "liberación
sostenida", "liberaciOn extendida" yb "liberación retardada". Las combinaciones de
Østas son posibles. El recubrimiento de liberación controlada puede comprender
opcionalmente otros materiales que pueden alterar la funcionalidad del recubrimiento de
20 liberación controlada. La expresión "liberación modificada" se usa indistintamente con
las expresiones "liberación controlada", "control de la liberaciOn" y "control de la
velocidad".

Las expresiones "barrera contra la humedad" y "recubrimiento de barrera contra la
1025 humedad", como Se usan aqul, se usan indistintamente y se defmen con el significado de
un recubrimiento que impide o retarda la absorción de la humedad. Se sabe que las sales
de bupropion son higroscOpicas y, como tales, son sensibles a la descomposición con el transcurso del tiempo en condiciones de humedad elevada. Otros fÆrmacos activos
tambiØn pueden ser susceptibles a la descomposición con ci tiempo en condiciones de
30 humedad elevada. La proporciOn de los componentes de la barrera contra la humedad y la
cantidad de barrera contra la humedad aplicada sobre ci recubrimiento de liberación controlada es tal que la barrera contra la humedad no estÆ comprendida por la definición
y los requisitos de la USP para un recubrimiento entØrico. Adecuadamente, la barrera
contra la humedad estÆcompuesta de un polimero entØrico y/o acrIlico, adecuadamente
35 un polimero acrIlico, opcionalmente un plastificante y un potenciador de la penetraciOn.
El potenciador de la penetración es una sustancia hidrófila, que permite ci ingreso de
agua sin alteración fIsica del recubrimiento. La barrera contra la humedad puede
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contener ademÆs otrosexcipientes inertes convencionales, que pueden mejorar el procesamiento de la formulación de liberación extendida descrita aqul.

La expresión "recubrimiento entØrico", como se usa aqul, se define con ci significado de
5 un recubrimiento o barrera que se aplica a una forma farmacØutica que puede controlar la
ubicación en ci aparato digestivo en donde el o los fÆrmacos activosse absorben. Por ejemplo, un recubrimiento entØrico puede usarse para: (i) proteger el fÆrmaco de laacción destructiva de las enzimas o del ambiente de bajo pH del estómago; (ii) evitar las nÆuseas
o sangrados asociados con la irritación de la mucosa gÆstrica por parte del fÆrmaco; yb
10 (iii) administrar el fÆrmaco en forma no diluida desde el intestino. En base aestos
criterios, en ciertas realizaciones, la forma farmacØutica recubierta entØricamente puede considerarse como un tipo de forma farmacØutica de liberaciOn retardada. La diferencia
con las formas farmacØuticas de liberación sostenida es que, en Østas, la liberación del fÆrmacose extiende durante un periodo de tiempo para mantener niveles en sangre
15 terapØuticos y para reducir la incidencia de efectos colaterales causados por una rÆpida
liberación, mientras que con los recubrimientos entØricos, ci objetivo principal es
restringir la liberación del fÆrmaco a una region predeterminada del tracto
gastrointestinal. Los recubrimientos entØricos funcionan presentando una superficie que
es sustancialmente estable con un pH Æcido perose desintegra para permitir la liberaciOn
20 del fÆrmaco en ci intestino.

La expresiOn "polimero entØrico", como se usa en la presente, se define con ci significado
de una sustancia polimØrica que, cuando se usa en una formulaciOn de recubrimiento
entØrico, es sustancialmente insoluble y/o sustancialmente estable en condiciones Æcidas
25 que exhiben tin pH menor que 5 y que son sustancialmente solubles o pueden
descomponerse en condiciones que exhiben un p1-1 de aproximadamente 5 o mÆs.
Ejemplos no limitantes de dichos pollmeros entØricos incluyen carboximetiletilcelulosa, acetato flalato de celulosa, acetato succinato de celulosa, ftalato de metilcelulosa, ftalato
de hidroximetiletilcelulosa, ftalato de hidroxipropilmetilcelulosa, acetato succinato de
30 hidroxipropilmetilcelulosa, ftalato de polivinil alcohol, ftalato de polivinil butirato, ftalato
de polivinil acetal, un copolimero de vinil acetato/anhidrido maleico, un copolimero de vinilbutilØter/anhidrido maleico, tin copolimero de estireno/monoØster de Æcido maleico,
tin copolimero de metil acrilato/Æcidometacrilico, tin copolimero de estireno/ªcido
acrilico, un copolimero de metil acrilato/Æcidometacrilico/acrilato de octilo, tin
35 copolimero de Æcidometacrilico/metil metacrilato y sus mezcias. Los polimØros entØricos
pueden utilizarse individualmente o en combinaciOn con otros poilmeros hidrófobos o hidrófilos en tin recubrimiento entØrico, un rnicieo de la matriz de liberaciOn normal, un

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niicleo de la matriz de liberación controlada y/o en un recubrimiento de liberación controlada. Los poilmeros entØricos pueden combinarse con otros excipientes farmacØuticamente aceptables para facilitar el procesamiento de un recubrimiento que comprende el poilmero entØrico o para alterar la funcionalidad del recubrimiento.

La expresión "recubrimiento funcional", como se usa aqul, se define con ci significado de
un recubrimiento que afecta la velocidad de iiberación in vitro o in vivo del o de los fÆrmacosactivos.

10 La expresión "recubrimiento no funcional", como se usa aqul, se define con el
significado de un recubrimiento que no afecta sustancialmente la velocidad de liberación
in vitro o in vivo del fªrmaco activo, pero puede mejorar las earacterIsticas qulmicas, bioiogicas y de estabilidad fisica o ci aspecto fisico de la forma farmacØutica de
liberación modificada.
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El tØrmino "niicleo", como se usa aquI, se define con ci significado de un vehIculo sólido
en ci cual al menos un fÆrmaco activose dispersa uniformemente o no uniformemente.
El nücleo puede formarse mediante mØtodos y materiales bien conocidos en la tØcnica,
como pot ejemplo, compresión, fusion o extrusion del fÆrmacoactivo junto con al menos
20 un excipiente farmacØuticamente aceptable. El nócleo puede fabricarse para format, por
ejempio, un nilcieo unitario homogØneo o no homogeneo, una muitipartleula o una pluralidad de micropartleulas comprimidas para format un nücieo unitario. Ejempios no limitantes de nücleos ineluyen rn.cleos de micropartleulas, nücleos de matriz y nücleos osmóticos. El o los nücleos pueden recubrirse con al menos un recubrimiento funcional
1025 Y/o un recubrimiento no funcional.

Las expresiones "nücleo de la matriz de liberaciOn modificada", "nücieo de la matriz de liberación controlada" o "nücieo de la matriz", cuando se hace referencia a una forma farmacØutica de la matriz de liberación controlada, como se usan aqul, se usan
30 indistintamente y se definen con ci significado de un nücleo en ci cual al menos un
fÆrmaco activose dispersa dentro de una matriz que controla o retrasa la liberación del fÆrmacoactivo durante un perlodo de 24 horas para permitir que una composición que comprende un nücleo de la matriz de iiberaciOn modificada se administre como una composición de una vez a! dIa. La velocidad de liberación del fÆrmaco activo desde ci
35 nücieo de la matriz de liberación modificada puede ser modificada por la porosidad y
tortuosidad de la matriz (es decir, la estructura de los poros). La adiciOn de sales, solutos
o agentes filamentosos puede influir en la velocidad de iiberaciOn, al igual que la

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manipulación de los parÆmetros de procesamiento. For ejemplo, la fuerza de compresiOn utilizada en la fabricación del nüeleo de la matriz de liberaeión modificada puede alterar
la porosidad del nicleo de la matriz y, por lo tanto, la velocidad de liberación del fÆrmaco activo. Los expertos en la tØcnica de la administración de fÆrmacos comprenderÆnque
5 una matriz mÆsrIgida serÆ menos porosay, por lo tanto, liberarÆel farmaco activo mÆs
lentamente en comparación con un nücleo de matriz de liberación modificada menos
rigido. El nücleo de la matriz de liberación modificada puede comprender formas farmacØuticas de la matriz insolubles o inertes, formas farmacØuticas de la matriz
hinchables, formas farmacØuticas de la matriz hinchables y erosionables, formas
10 farmacØuticas de la matriz bidrOfobas, formas farmacØuticas de la matriz hidrófilas,
formas farmacØuticas de la matriz erosionables, formas farmacØuticas de reservorio o cualquier combinación de sus combinaciones. El nücieo de la matriz de liberación modificada puede comprender al menos una matriz insoluble, al menos una matriz hinchable, al menos una matriz hinchable y erosionable, al menos una matriz hidrOfoba,
15 al menos una matriz hidrófila, al menos una matriz erosionable, o una combinación de
Østas, en donde la velocidad de liberación es mÆs lenta que lade las formas farmacØuticas
de liberación inmediata sin recubrir. Los nücleos de la matriz de liberación modificada pueden recubrirse con al menos un recubrimiento de liberación controlada para ralentizar atm mÆs la liberación del fÆrmaco activodel ntmcleo de la matriz de liberación

20 modificada. Dichos ntmcleos de la matriz de liberación modificada recubiertos pueden
presentar liberación modificada, liberaciOn controlada, liberación sostenida, liberación
extendida, liberación prolongada, liberación bifÆsica, liberaciOnretardada o
combinaciones de Østas del fÆrmacoactivo. Los ntmcleos de la matriz de liberación modificada tambiØn pueden estar recubiertos con un recubrimiento soluble no funcional.

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El tØrmino "plastificante" como se usa aquf incluye todos los compuestos capaces de plastificar o ablandar un polimero o un aglutinante usados en la presente invención. El
uso de plastificantes es opcional y puede estar incluido en la forma farmacØutica para
modificar las propiedades y las caracteristicas de los polImeros usados en ci o los
30 recubrimientos o en el ntmcleo de la forma farmacØutica para el procesamiento
conveniente durante la fabricación del o los recubrimientos y/o del ntmcleo de la forma farmacØutica. Una vez que se prepararon el o los recubrimientos y/o el ntmcleo, ciertos plastificantes pueden actuar para aumentar la hidrofilicidad del o de los recubrimientos
y/o del ntmcleo de la formÆfarmacØutica en el ambiente de uso. Durante la fabricaciOn del
35 o los recubrimientos yio ci ntmcieo, ci piastificante puede reducir la temperatura de fusiOn
o la temperatura de transición vitrea (temperatura del punto de ablandamiento) del
polimero o aglutinante. Pueden incluirse plastificantes con un polImero y reducir su

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temperatura de transición vItrea o punto de abiandamiento. Los plastifleantes tambiØn pueden reducir la viscosidad de un poilmero. Los piastificantes pueden impartir aigunas propiedades fisicas particularmente ventajosas a las formas farmacØuticas de la
invención.

Las expresiones "formador de poros", "agente formador de poros" y "aditivo formador de poros", como Se usan aqul, se usan indistintamente en esta solicitud y se definen con ci significado de un excipiente que puede agregarse a un recubrimiento (por ejemplo, ci recubrimiento de liberaciOn controlada), en donde al exponerse a los fluidos del ambiente
10 de uso, el formador de poros se disuelve o lixivia del recubrimiento para formar poros,
canales o caminos en ci recubrimiento que pueden lienarse con ci lIquido ambiental y permitir que ci mismo entre en ci nücleo, disuelva el fªrmaco activo y modifique las caracteristicas de liberación de la formulación. Los fonnadores de poros pueden ser inorganicos u orgÆnicos e incluyen materialesque se pueden disolver, extraer o lixiviar
15 del recubrimiento en ci ambiente de uso.

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La expresión "estado estacionario", como se usa aqul, significa que la curva de concentraciOn plasmÆtica ensangre para un determinado fÆrmacono fluctüa sustancialmente luego de dosis repetidas de la formulación.

"AUC", como se usa aqui, significa un area debajo de la curva de concentración plasmÆtica-tiempo,segæn se calcula mediante Ia regla trapezoidal en un intervalo de tiempo (por ejemplo, un intervalo compieto de 24 horas); y significa ci grado de absorción de un fÆrmaco.

"CmÆx", como seusa aqul, significa la mayor concentración plasmÆtica del fÆrmaco obtenida dentro del intervalo de dosificación (por ejemplo, 24 horas).

"CmIn", como se usa aquf, significa la minima concentración plasmÆticadel fÆrmaco
30 obtenida dentro del intervalo de dosificación (por ejemplo, 24 horas).

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"Cprom", como se usa aquI, significa la concentraciOn p!asmÆticadel fÆrmacodentro del intervalo de dosificación (por ejemplo, 24 horas), y se caicula como AUC/intervalo de dosificación.

"TmÆx",como se usa aqul, significa ci perlodo de tiempo que transcurre luego de la administraciOn de la forma farmacØutica en ci cual la concentración piasmÆtica del

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fªrrnaco alcanza su concentración plasmÆtica mªs alta de fÆrmaco obtenidadentro del intervalo de dosificaciOn (por ejemplo, 24 horas).

El tØrmino "bioequivalencia", como se usa en la presente, se define como el hecho de que
5 haya aproximadarnente un 90% o rnÆs de probabilidad de que labiodisponibilidad (AUC)
del fÆnnaco activo segün se determina mediante mØtodos estÆndar sea de
aproximadarnente 80% a aproxirnadamente 125% de la segunda forma farrnacØutica administrable oralmente que comprende la misma dosis del fÆrmaco activoy como el
hecho de que haya aproximadainente un 90% o mÆs de probabilidad de que la
10 concentraciOn plasrnÆtica en sangre maxima(CmÆx) delfÆrmaco activo segün se mide
mediante mØtodos estÆndar es deaproxirnadamente 80% a aproxirnadamente 125% de la segunda forma farmacØutica administrable oralmente. Por ejemplo, Se remite al lector a
la version final de la gula aprobada por la AdministraciOn de Alimentos y FÆrmacos de
los Estados Unidos al momento de la presentación de esta solicitud de patente, es decir, la
15 version de marzo de 2003 de la Gula para la industria: Estudios de biodisponibilidad y
bioequivalencia para productos farmacØuticos administrados oralmente - consideraciones generales, Departarnento de Salud y Servicios Hurnanos de los Estados Unidos, Administración de Alimentos y FÆrmacos, Centro para la Evaluación e Investigación de FÆrmacos (CDER), por mÆs detalles en cuanto a la bioequivalencia.
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Las expresiones "un/a" o "al menos un/a", como se usan aqul, se usan indistintamente en
esta solicitud y se definen con el significado de "uno/a" o "uno/a o mÆs".
Los parÆmetrosnumØricos establecidos en la siguiente memoria descriptiva y las reivindicaciones adjuntas que estÆn modificados por el tØrmino"aproximadamente" son
W25 aproximaciones que pueden variar, dependiendo de las propiedades tecnolOgicas de cada
caso en particular. Por ejemplo, el tØrmino "aproxirnadamente" puede significar dentro de
un intervalo de error aceptable (por ejemplo, desviaciones estÆndar)para el valor
particular determinado por un tØcnico con experiencia en el tema, que dependerÆ en parte
de cOmo se mide o determina el valor, por ejemplo, de las limitaciones del sistema de
30 mediciOn.

Otros tØrminos se definen segün aparecen en la descripciOn siguiente y Se deben
interpretar en el contexto en el cual aparecen.

La presente invención abarca la sal broinhidrato de bupropion y composiciones que
35 contienen niveles eficaces de la sal bromhidrato de bupropion que pueden utilizarse para
el tratamiento de una afección en sujetos que pueden beneficiarse de la administración de bupropion, en donde la sal brornhidrato de bupropion y las composiciones que contienen

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niveles eficaces de la sal bromhidrato de bupropion inesperadamente reducen las incidencias y/o la gravedad de las crisis convulsivas inducidas por bupropion, y son mÆs estables, en comparación con cantidades molares equivalentes de clorhidrato de
bupropion o composiciones por lo demÆs similares oidØnticas que contengan cantidades molares equivalentes de clorhidrato de bupropion.

AdemÆs, lapresente invención abarca sus polimorfos y formas enantiomØricas
purificadas especificas. La presente invención tambiØn abarca ci uso de dicha sal bromhidrato de bupropion y composiciones que contienen la sal bromhidrato de
10 bupropion para ci tratamiento de una o mÆs afecciones enan sujeto adecuado para el
tratamiento con bupropion o sus sales farmacØuticamente aceptables (por ejemplo, depresión, obesidad, adicción a la nicotina y otras afecciones tratables con bupropion
como se divulga aqul); en donde las incidencias y/o gravedad de las crisis convulsivas inducidas por bupropion se reducen en comparación con una cantidad molar equivalente
15 de clorhidrato de bupropion u otra eomposición por lo demÆs similar o idØnticaque
contenga una cantidad molar equivalente de clorhidrato de bupropion.

La presente invención abarca todo medicamento que contiene una cantidad farmacØuticamente eficaz de bromhidrato de bupropion Esto inciuye medicamentos
20 administrables tanto por via oral como no oral como medicamentos tópicos, inyectabies,
aerosoles y otros medicamentos inhalables. En particular, dichas composiciones de medicamentos incluyen formas farmacØuticas de liberación modificada administrables
por via oral que contienen ci bromhidrato de bupropion. Las dosis se pueden presentar de manera conveniente en formas farmacØuticas unitarias y se pueden preparar por
4925 cuaiquiera de los mØtodos conocidos en el area farmacØutica. Una "forma farmacØutica
sólida" como se usa aqul, significa una forma farmacØutica que no es ni liquida ni
gaseosa. Las formas farmacØuticas incluyen formas farmacØuticas sóiidas, como
comprimidos, polvos, micropartIculas, cÆpsulas, supositorios,sobres, trociscos, parches y pastilias asI como suspensiones lIquidas y elixires. Las capsulas contienen la
30 composición sólida dentro de una cÆpsula quepuede hacerse de gelatina u otro material
de encapsulado convencional.

Las formas farmacØuticas de liberación modificada contempladas en la presente
invención pueden ser muitiparticuladas o monolIticas. Por ejemplo, los tØcnicos con
35 experiencia en ci area farmacØutica y el diseflo de medicamentos estÆnal tanto de las
matrices de liberación modificada convencionalmente usadas en las composiciones

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farmacØnticas orales adoptadas path la liberación modificada y de los medios para su preparación.

Una formulación de liberaciOn modificada que contiene el bromhidrato de bupropion de
5 acuerdo con la presente invenciOn se puede recubrir con uno o rnÆsrecubrimientos
funcionales o no funcionales. Los ejemplos no limitantes de recubrimientos funcionales incluyen recubrimientos polimØricos de liberación controlada, recubrimientos de barrera contra la humedad, recubrimientos polimØricos entØricos y similares. En al menos una realización de la presente invención, una composición de bromhidrato de bupropion
10 comprende un recubrirniento polirnØrico de liberación controlada que incluye un
polirnero acrilico. Los poilmeros acrIlicos adecuados incluyen, pero no exciusivamente, copolimeros del Æcido acrilicoy el ÆcidometaerIlico, copolimeros de metacrilato de
metilo, metacrilatos de etoxietilo, metacrilato de cianoetilo, copoilmero de metacrilato de aininoalquilo, poli(Æcido acrilico), poli(ÆcidometacrIlico), copolimero de dcido
15 metacrilico alquilamina, poli(metacrilato de metilo), poli(ÆcidometacrIlico) (anhidrido),
poliacrilamida, poli(anhIdrido del ÆcidometacrIlico), copolimeros de metacrilato de
glicidilo y sus mezclas.

En al menos una realizaciOn se emplean compuestos de amonio cuaternario
20 polimerizables en el recubrirniento de liberación controlada, de los cuales los ejemplos no
limitantes incluyen Østeres aminoalquilicos y aminoalquilamidas cuaternizados del Æcido acrilico y el ÆcidometacrIlico, por ejemplo metosulfato de f3metacril-oxietil-trimeti1-
arnonio, cloruro de 13-acriloxi-propil-trirnetil-amonio, metosulfato de trimetilaminometil-

18 metacrilamida y sus mezclas. El Ætornode amonio cuaternario tambiØn puede form.ar
25 parte de un heterociclo, como en el cloruro de metacriloxietilmetil-morfolinio o la
correspondiente sal de piperidinio, o se puede unir a tin grupo Æcido acrIlico o a ungrupo
Æeido metacrIlicoa travØs de tin grupo que contiene heteroÆtomos,como un grupo Øter poliglicólico. Otros compuestos de amonio cuaternario polimerizables adecuados
incluyen heterociclos de nitrógeno cuaternizados sustituidos con vinilo como las sales de
30 metilvinil piridinio, los ºsteres de vinilo de Æcidos amino carboxilicoscuaternizados, las
sales de estiriltrialquilamonio y sus mezclas. Otros compuestos de amonio cuaternario polimerizables iitiles en la presente invención incluyen cloruro y metosulfato de acril- y rnetacril-oxietiltrirnetilamonio, cloruro de bencildimetilamoniornetil-metacrilato,
metosulfato de dietilrnetilamoniometil-aerjlato y -metacrilato, cloruro de N-
35 trimetilarnoniopropilmetacrilamida, cloruro de N-trimetilamonio-2,2-dimetilpropil- 1-
metacrilato y sus mezclas.

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En al menos una realización, el poilmero acrilico del recubrimiento de liberación controlada estÆ compuesto deurio o mÆscopolImeros de metacrilato de amonio. Los copoilmeros de metacrilato de amonio (por ejemplo, EUDRAGITfi RS y RL) se describen en ci National Formulary (NF) XVII como copolImeros totalniente
polimerizados de Østeres de Æcido aerflicoy metacrIlico con un contenido bajo de grupos amonio cuaternario. Pueden incorporarse dos o mÆs copolimerosde metacrilato de
amonio que tengan propiedades fisicas diferentes en el recubrimiento de liberación controlada de ciertas realizaciones. Por ejemplo, se sabe que cambiando la relación
molar entre los grupos de amonio cuaternario y los Østeres (met)acrIlieos neutros, se
10 pueden modificar las propiedades de permeabilidad del recubrimiento resultante.

En ciertas realizaciones adicionales de la presente invención, el recubrimiento de
liberación controlada incluye ademÆsun poilmero cuya permeabilidad es dependiente del pH, como los polImeros aniónicos sintetizados a partir del ÆcidometacrIlico y el ester
15 metIlico del Æcido metacrIlico(pot ejemplo, EUDRAGITfi L y EUDRAGITfi S). Se
sabe que la relación entre los grupos carboxilo libres y los Østeres es 1:1 en
EUDRAGITfi L y 1:2 en EUDRAGITfi S. EUDRAGITfi L es insoluble en Æcidosy
agua pura, pero se torna cada vez mÆs permeable por encima depH 5,0. EUDRAGITfi S
es similar, excepto que se torna cada vez mÆspermeable por encima de pH 7. Los
20 recubrimientos de poilmero acrIlico hidrófobo tambiCn pueden incluir un polImero con
catheter catiónico a base de metacrilato de dimetilaminoetilo y Csteres del Æeido
metacrIlico neutros (por ejemplo, EUDRAGITfi E). Los recubrimientos de polimero
acrIlico hidrOfobo de la presente invención pueden incluir ademÆsun copoilmero neutro a
base de poli(met)acrilatos, como EUDRAGITfi NE. Las pelIculas de laca de
1025 EUDRAGITfi NE 30D son insolubles en agua y lfquidos digestivos, pero permeables e
hinchables.

En al menos otra realización de la invención, el recubrimiento de liberaciOn controlada comprende una dispersion de poli(etilacrilato, metacrilato de metilo) 2:1
30 (KOLLICOATfi EMM 30 D).

En al menos otra realización de la invención, el recubrimiento de liberación controlada comprende un acetato de polivinilo estabilizado con polivinilpirrolidona y lauril sulfato
de sodio, tal como KOLLICOATfi SR30D. El perfil de disolución se puede alterar
35 cambiando las cantidades relativas de diferentes lacas de resina acrilica incluidas en el
recubrimiento. Tambien, cambiando la re!ación molar entre ci agente polimerizable que mejora la permeabilidad (por ejemplo, los compuestos de amonio cuaternario) y los

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Østeres (met)aerulicos neutros, se pueden modiflear las propiedades de permeabilidad (y
por lo tanto el perfil de disoluciOn) del recubrimiento resultante.

En at menos una realización de la invención, el recubrimiento de liberaciOn controlada
5 comprende etilcelulosa, que se puede usar como un polimero seco (por ejemplo,
ETHOCELfi) solubilizado en disolvente orgÆnico antesde usar, 0 como una dispersion acuosa. Una dispersion acuosa comercialmente disponible de etilcelulosa es AQUACOATfi. El AQUACOATfi se puede preparar disolviendo la etilcelulosa en un disolvente orgÆnico inmiscible conagua y luego emulsionar el mismo en agua en
10 presencia de un tensioactivo y un estabilizador. DespuØs de la homogeneización para
generar gotitas submicrOnicas, el disolvente organico se puede evaporar al vaclo para
formar un pseudolªtex. El plastificante no se incorpora en el pseudolÆtexdurante la fase
de fabricaciOn. Por lo tanto, antes de usar el mismo como un recubrimiento, se puede mezelar ci AQUACOATfi intimamente con un plastificante adecuado. Otra dispersion
15 acuosa adecuada de etilcelulosa se encuentra comercialmente disponible como
SURELEASEfi. Este producto se puede preparar incorporando un plastificante en la dispersion durante el proceso de fabricaciOn. Puede prepararse una masa fundida caliente
de un poilmero, un plastificante (por ejemplo, sebacato de dibutilo) y un estabilizador
(por ejemplo, Æcido oleico) comouna mezcla homogØnea, que luego se puede diluir con
20 una solución alcalina para obtener una dispersiOn acuosa que se puede aplicar
directamente sobre los sustratos.

Otros ejemplos de polimeros que se pueden usar en ci recubrimiento de iiberación
. controlada incluyen ftalato acetato de celulosa, trimaleato acetato de celulosa, ftaiato de
25 hidroxipropilmetilcelulosa, ftaiato acetato de polivinilo, flalato de alcohol polivinflico,
laca; hidrogeles y materiales que forman geles, como polimeros carboxivinilicos, alginato
de sodio, carmelosa de sodio, carmelosa de caleb, carboximetil almidOn sOdico, alcohol polivinilico, hidroxietilcelulosa, metilcelulosa, etilcelulosa, gelatina, almidón y polimeros reticulados a base de celulosa en los que ci grado de reticulación es bajo para facilitar la
30 adsorción de agua y la expansion de la matriz del polImero, hidroxipropilcelulosa,
hidroxipropilmetilcelulosa, polivinilpirrolidona, almidOn reticulado, celulosa
microcristalina, quitina, pullulan, coiÆgeno,caseina, agar, goma arÆbiga, carboximetilcelulosa sOdica, (polimeros hidrOfilos hinchables)
poli(hidroxialquilmetacriiato) (peso molecular de aproximadamente 5 k a
35 aproximadamente 5.000 k), polivinilpirrolidona (peso molecular de aproximadamente 10
k a aproximadamente 360 k), hidrogeles aniónicos y catiónicos, zeina, poliamidas, alcohol polivinflico con bajo contenido de acetato residual, una mezcla hinchabie de agar

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y carboximetilcelulosa, copoilmeros de anhIdrido maleico y estireno, etileno, propileno o isobutileno, pectina (peso molecular de aproximadamente 30 k a aproximadamente 300
k), polisacÆridos como agar,acacia, karaya, tragacanto, alginas y guar, poliacrilamidas,
ó xidos de polietileno POLYOXfi (peso molecular de aproximadamente 100 k a
5 aproximadamente 5.000 k), polimeros de acrilato AQUAKEEPfi, diØsteres de
poliglucano, alcohol polivinIlico y poli N-vinil-2-pirrolidona reticulados, polimeros hidrófilos como los polisacaridos, metilcelulosa, carboximetilcelulosa de sodio o de
calcio, hidroxipropilmetilcelulosa, hidroxipropilcelulosa, hidroxietilcelulosa,
nitrocelulosa, carboximetilcelulosa, Øteres de celulosa, metiletilcelulosa,
10 etilhidroxietilcelulosa, acetato de celulosa, butirato de celulosa, propinionato de celulosa,
gelatina, almidón, maltodextrina, pullulan, polivinilpirrolidona, alcohol polivinflico,
acetato de polivinilo, Østeres de Æcidosgrasos de glicerol, poliacrilamida, Æcido
poliacrIlico, gomas naturales, lecitinas, pectina, alginatos, alginato de amonio, alginatos
de sodio, calcio y potasio, alginato de propilenglicol, agar y gomas como arªbiga, karaya,
15 de algarrobo, tragacanto, carrageninas, guar, xantano, escieroglucano y sus mezclas.

En al menos una realización, las formas farmacØuticas se recubren con polimeros para facilitar la adhesion a la mucosa del aparato digestivo. Ej emplos no limitantes de
polimeros que se pueden usar para la adhesion a la mucosa incluyen
20 carboximetilcelulosa, ÆcidopoliacrIlico, CARBOPOLTM, POLYCARBOPHILTM,
gelatina, otros poilmeros naturales o sintØticos y sus mezclas.

En al menos una realización de la invención, la forma farmacØutica es un comprimido de liberación extendida que comprende: (i) un nücleo que incluye bromhidrato de bupropion
1025 en una cantidad de aproximadamente 40% a aproximadamente 99% en peso del peso
seco del comprimido, incluidos todos los valores y rangos intermedios, un aglutinante
como el alcohol polivinflico en una cantidad de aproximadamente 0,5% a
aproximadamente 25% en peso del peso seco del comprimido, incluidos todos los valores
y tangos intermedios, y un lubricante como el behenato de glicerilo en una cantidad de
30 aproximadamente 0,1% a aproximadamente 5% en peso del peso seco del comprimido,
incluidos todos los valores y tangos intermedios; y (ii) un recubrimiento de liberación controlada que incluye un polImero formador de peilcula insoluble en agua y permeable
al agua como etilcelulosa en. una cantidad de aproximadamente 1% a aproximadamente
12% en peso del peso seco del comprimido, incluidos todos los valores y rangos
35 intermedios, un polImero soluble en agua como polivinilpirrolidona (POVIDONEfi USP)
en una cantidad de aproximadamente 1,5% a 10% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios, opcionalmente un plastificante como

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sebacato de dibutilo, el polietilenglicol 4000 o una rnezcla de Østos en una cantidad de aproximadamente 0,5% a aproximadamente 4% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios, y opcionalmente una cera como la cera carnauba en una cantidad de aproximadamente 0,01% a aproximadamente 0,05% en peso
del peso seco del comprimido, incluidos todos los valores y rangos intermedios.

En al menos una realizaciOn de la inveneión, la forma farmacØutica es un comprimido de !iberación extendida de 174 mg que comprende: (i) un nücleo que incluye brornhidrato de bupropion (por ejemplo, aproximadamente 81% en peso del peso seco del comprimido),
10 un aglutinante como el alcohol polivinilico (por ejemplo, aproximadamente 3% en peso
del peso seco del comprimido) y un lubricante como el behenato de glicerilo (por
ejemplo, aproximadamente 3% en peso del peso seco del comprimido); y (ii) un
. recubrimiento de liberaciOn controlada que incluye un poilmero formador de peilcula,
insoluble en agua y permeable al agua como etilcelulosa (por ejemplo, aproximadamente
15 7% en peso del peso seco del comprimido), un poilmero soluble en agua como
polivinilpirrolidona (POVIDONEfi USP), (pot ejemplo, aproximadamente 4% en peso
del peso seco del comprimido), opcionalmente un plastificante como sebacato de
dibutilo, polietilenglicol 4000 o una mezcla de Østos (por ejemplo, aproximadamente 2%
en peso del peso seco del comprimido) y opcionalmente una cera como cera carnauba
20 (pot ejemplo, aproximadamente 0,03% en peso del peso seco del comprimido).

En al menos una realización de la invención, la forma farmacØutica es un comprimido de liberación extendida de 348 mg que comprende: (i) un nücleo que incluye bromhidrato de bupropion (por ejemplo, aproximadamente 87% en peso del peso seco del comprimido),
25 un aglutinante como el alcohol polivinflico (por ejemplo, aproximadamente 3% en peso
del peso seco del comprimido) y un lubricante como el behenato de glicerilo (por
ejemplo, aproximadamente 3% en peso del peso seco del comprimido); y (ii) Ufl recubrimiento de liberación controlada que incluye un polfmero fonnador de pelicula, insoluble en agua y permeable al agua como etilcelulosa (por ejemplo, aproximadamente
30 4% en peso del peso seco del comprimido), un poilmero soluble en agua como
polivinilpirrolidona (POVIDONEfi USP), (pot ejemplo, aproximadamente 2% en peso
del peso seco del comprimido), opcionalmente un plastificante como sebacato de
dibutilo, polietilenglicol 4000 o una rnezcla de Østos (por ejemplo, aproximadamente 1%
en peso del peso seco del comprimido) y opcionalmente una cera como cera carnauba
35 (por ejemplo, aproximadamente 0,01% en peso del peso seco del comprimido).

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En al menos una realización de la invención, la forma farmacØutica es un comprimido XL
de 522 mg que comprende: (i) un nücleo que incluye bromhidrato de bupropion (por ejemplo, aproximadamente 85% en peso del peso seco del comprimido), un aglutinante
como el alcohol polivinilico (por ejemplo, aproximadamente 3,5% en peso del peso seco del comprimido) y un lubricante como el behenato de glicerilo (por ejemplo, aproximadamente 3,5% en peso del peso seco del comprimido); y (ii) un recubrimiento de liberación controlada que incluye un poilmero formador de pelIcula, insoluble en agua y permeable al agua como etilcelulosa (por ejemplo, aproximadamente 3% en peso del peso seco del comprimido), un polimero soluble en agua como polivinilpirrolidona (POVIDONEfi USP), (por ejemplo, aproximadamente 3,5% en peso del peso seco del comprimido), opcionalmente un plastificante como sebacato de dibutilo, polietilenglicol 4000 o una mezcla de Østos (por ejemplo, aproximadamente 1,5% en peso del peso seco del comprimido) y opcionalmente una cera como cera carnauba (por ejemplo, aproximadamente 0,01% en peso del peso seco del comprimido).

AdemÆs de las formasfarmacØuticas de liberación modificada descritas en la presente, pueden usarse otras tecnologIas de liberación modificada conocidas por los expertos en la tØcnica con el fin de obtener las formulaciones de liberación modificada de ciertas realizaciones de la presente invención. Diehas formulaciones se pueden fabricar como una formulación oral de liberación modificada, por ejemplo, en tin comprimido adecuado o una formulación multiparticulada conocida por los tØcnicos con experiencia en el tema. En cualquier caso, la forma farmacØutica de iiberaeión modificada puede incluir opcionalmente un vehiculo de liberación controlada que se incorpora en una matriz junto con el fÆrmaeo oque se aplica como un recubrimiento de liberación controlada.

Comprimidos
En ciertas realizaciones de la presente invenciOn, se proporciona un comprimido de liberación modificada que tiene un nücleo que comprende bromhidrato de bupropion y excipientes convencionales, en donde la sal bromhidrato de bupropion o la composición que comprende el bromhidrato de bupropion proporciona una reducciOn de las incidencias y/o gravedad de las crisis convulsivas inducidas por bupropion, y es rnÆs estable en comparación con cantidades molares equivalentes de ciorhidrato de bupropion o composiciones por lo demÆs similares o idØnticas quecontengan cantidades molares equivalentes de clorhidrato de bupropion. El nücleo puede estar rodeado por un recubrimiento de liberación controlada que puede controlar la liberación del bromhidrato de bupropion o la mezcla de bromhidrato de bupropion con un segundo fÆrmaco. En otras realizaciones, se puede agregar opcionalmente una barrera contra la humedad para

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rodear el recubrimiento de liberaciOn controlada. Esta barrera contra la humedad es
opcional dada la estabilidad mejorada del brornhidrato de bupropion eon relaeión al
clorhidrato de bupropion y por selección de recubrimientos de liberación controlada apropiados. Si estÆ presente,esta barrera contra la humedad puede afectar a la liberación de fÆrmacos in vitro asicomo evitar que la hurnedad entre en contacto con la sal brornhidrato de bupropion. Opcionalrnente, este comprimido puede comprender, ademÆs, uno o mÆs recubrimientosfuncionales o no funcionales adicionales airededor del nücleo, la barrera contra la humedad y/o el recubrimiento de liberación controlada.

Comprimidos de liberaciOn extendida (XL)
En ciertas realizaciones de la presente invención, se proporciona un comprimido de liberación extendida (XL) que tiene un nücleo que comprende bromhidrato de bupropion y excipientes convencionales, en donde la sal bromhidrato de bupropion proporciona una reducción de las incidencias y/o de la gravedad de las crisis convulsivas inducidas por bupropion, y es mÆs estable,en comparación con cantidades molares equivalentes de elorhidrato de bupropion. El nücleo se puede rodear con un recubrimiento de liberaeión controlada que controla la liberación de la sal bromhidrato de bupropion. El comprimido puede comprender opeionalmente uno o mÆs recubrimientos funcionales o nofuncionales adicionales airededor del nücleo o ci recubrimiento de liberación controlada. El comprimido de iiberación extendida de ciertas realizaciones tiene una inesperada estabilidad mej orada.

El nücleo XL

El nücleo del comprimido de liberaeión extendida comprende una cantidad eficaz de la sal bromhidrato de bupropion, un aglutinante y un lubricante y puede contener otros excipientes inertes convencionales. La cantidad de sal bromhidrato de bupropion presente en el nücleo XL puede variar en una cantidad entre aproximadamente 40% y aproximadamente 99% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, ci bromhidrato de bupropion estÆ presente en unacantidad entre aproximadamente 70% y aproximadamente 95% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios. Por ejernp!o, en ciertas realizaciones, el nücleo comprende bromhidrato de bupropion en una proporción de aproximadamente 40%, aproximadamente 45%, aproximadamente 50%, aproximadamente 55%, aproximadamente 60%, aproximadamente 65%, aproximadarnente 70%, aproximadamente 75%, aproximadamente 80%, aproximadamente 85%, aproximadamente 90%, aproximadamente 95% o aproximadamente 99% del peso en seco del ntcieo.

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En al menos una realización de un comprimido de 174 mg de dosis, el bromhidrato de bupropion estÆpresente en una cantidad entre aproximadamente 75% y aproximadamente 85% en peso del peso seco del comprimido, incluidos todos los valores y rangos
5 intermedios. En al menos una realización de un comprimido de 348 mg de dosis, el
bromhidrato de bupropion puede estar presente en una cantidad entre aproximadamente
80% y aproximadamente 90% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios. En al menos una realizaciOn de un comprimido de 522 mg
de dosis, el bromhidrato de bupropion estÆpresente en una cantidad entre
10 aproximadamente 75% y aproximadamente 90% en peso del peso seco del comprimido,
incluidos todos los valores y rangos intermedios. En ciertas realizaciones de los comprimidos de bromhidrato de bupropion de liberación extendida de 174 mg, 348 mg y
522 mg de dosis, la cantidad de bromhidrato de bupropion presente es de
aproximadamente 85% a aproximadamente 99% en peso del nücleo seco para cada dosis,
15 incluidos todos los valores y rangos intermedios.

Se puede agregar un aglutinante (tambiØn denominado a veces adhesivo) a una mezela de relleno y fÆrmacopara aumentar la fuerza mecÆnicade los grÆnulosy los comprimidos durante la formación. Los aglutinantes se pueden agregar a la formulaeión de diferentes
20 maneras; (1) como un polvo seco, que se mezcla con otros ingredientes antes de la
aglomeraciOn hümeda, (2) como una solución, que se usa como liquido de aglomeraciOn
durante la aglomeración hümeda, y se denomina solución aglutinante, y (3) como un
polvo seco, que se mezela con los otros ingredientes antes de la compactación. En esta
forma el aglutinante se denomina aglutinante seco. Las soluciones aglutinantes son una
1025 manera comün de incorporar un aglutinante a los grÆnulos. En ciertas realizaciones, el
aglutinante usado en los comprimidos XL estÆ enforma de una solución aglutinante.
Ejemplos no limitantes de aglutinantes Utiles para el nücleo incluyen aceite vegetal hidrogenado, aceite de ricino, parafina, alcoholes alifÆticossuperiores, ÆcidosalifÆticos superiores, Æcidos grasosde cadena larga, Østeres de Æcidosgrasos, materiales similares a
30 cera como alcoholes grasos, Østeres de Æcidosgrasos, gliceridos de Æcidosgrasos, grasas
hidrogenadas, hidrocarburos, ceras normales, Æcido esteÆrico,alcohol estearIlico,
pollineros hidrófobos e hidrófilos que tienen esqueletos hidrocarbonados y sus mezelas. Ejemplos especIficos de polimeros solubles en agua aglutinantes incluyen almidón modificado, gelatina, polivinilpirrolidona, derivados de celulosa (como por ejemplo
35 hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa (HPC)), alcohol polivinIlico
y sus mezclas. La cantidad de aglutinante presente puede variar de aproximadamente
0,5% a aproximadamente 25% en peso del peso seco del comprimido, incluidos todos los

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valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, el aglutinante estÆ presente en una cantidad entre aproximadamente 0,5% y aproximadamente 15% en peso
del peso seco del comprimido, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones de los comprimidos de 174 mg, 348 mg y 522 mg de
5 dosis, el aglutinante estÆ presente en una cantidad entre aproximadamente 1% y
aproximadamente 6% en peso del peso de cada nücleo seco, incluidos todos los valores y rangos intermedios, y en otras realizaciones en aproximadamente 3% en peso del peso de cada nücleo seco. En al menos una realización del comprimido de 522 mg de dosis, ci aglutinante estÆpresente en una cantidad de aproximadamente 4% en peso del peso del
10 nücleo seco. En al menos una realización de la invención el aglutinante es el alcohol
polivinIlico.

Se pueden agregar lubricantes a las formulaciones farmacØuticas para reducir cualquier fricción que ocurra entre el sólido y la pared de la matriz durante la fabricación de
15 comprimidos. Una fricciOn elevada durante la compresión puede causar una serie de
problemas, entre otros una inadecuada calidad del comprimido (decapado o incluso fragmentacion de comprimidos durante la expulsion y rayones verticales en los bordes
del comprimido) y puede incluso detener la producciOn. Por lo tanto, los lubricantes se agregan a formulaciones en comprimidos de ciertas realizaciones del comprimido XL
20 descritas en la presente. Ejemplos no limitantes de lubricantes ütiles para ci nicleo
incluyen behenato de glicerilo, Æcido esteÆrico,aceites vegetales hidrogenados (como
aceite de semilla de algodón hidrogenado (STERPTEXfi), aceite de soja hidrogenado (STEROTEXfi HM) y aceite de soja hidrogenado y cera de ricino (STERPTEXfi K),
alcohol estearIlico, leucina, polietilenglicol (PM 1.450, adecuadamente 4.000 y mayor),
025 estearato de magnesio, monoestearato de glicerilo, ÆcidoesteÆrico, polietilenglicol,
polImeros de óxido de etileno (por ejemplo, CARBOWAXfi), lauril sulfato de sodio,
lauril sulfato de magnesio, oleato de sodio, estearil fumarato de sodio, DL-leucina, sIlice coloidal, sus mezelas y otros conocidos en ci area. En at menos una realización de la
presente invención, ci lubricante es behenato de glicerilo (por ejemplo, COMPRITOLfi
30 888). La cantidad de lubricante presente puede variar de aproximadamente 0,1% a
aproximadamente 6% en peso del peso seco del comprimido, incluidos todos los valores
y rangos intermedios. Por ejemplo, en ciertas realizaciones, la cantidad de lubricante presente es de aproximadamente 2% a aproximadamente 3% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios; y en otras realizaciones la
35 cantidad de lubricante presente es aproximadamente 3% en peso del peso seco del
comprimido. En ciertas realizaciones de los comprimidos XL de la invención de 174 mg, 348 mg y 522 mg de dosis, ci lubricante estÆpresente en una cantidad de

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aproximadamente 3% en peso del peso seco del comprimido, o de aproximadamente 1% a aproximadamente 6% en peso del peso seco del rniicleo, incluidos todos los valores y ranos intermedios. Por ejemplo, en ciertas realizaciones el lubricante estª presente en
una cantidad de aproximadamente 3% en peso del peso seco del niicleo para los comprimidos XL de 174 mg, 348 mg y 522 mg de dosis. En al menos una realización del comprimido de 522 mg de dosis, el lubricante estÆ presente en unacantidad de aproximadamente 4% en peso del peso del nüeleo seco.

En esta etapa, la formulación del ncicleo XL de ciertas realizaciones de la presente
10 invenciOn, es una formulación de liberaciOn inmediata sin recubrimiento que da lugar a
una disolución de aproximadamente 100% de la sal bromhidrato de bupropion en el transcurso de 1 hora. En al menos una realización el nIcleo XL es una formulación de
matriz de liberación normal. En ciertas realizaciones el nücleo comprende una cantidad farmacØuticamente eficaz de bromhidrato de bupropion, un aglutinante (por ejemplo,
15 alcohol polivinilico) y un lubricante (por ejemplo, behenato de glicerilo). Otros
excipientes inertes compatibles con los objetivos de hi invención tambiØn se pueden
agregar a la formulaciOn del nücleo. Los excipientes inertes adicionales se pueden
agregar para facilitar la preparaciOn y/o mejorar la aceptación por parte del paciente de la
forma farmacØutica de liberación extendida final segiin se describe aqul. Los excipientes
20 inertes adicionales son bien conocidos por los tØcnicos con experiencia y se pueden
encontrar en la bibliograffa pertinente, por ejemplo en el Handbook of Pharmaceutical Excipients. Ejemplos no limitantes de tales excipientes incluyen lactosa secada por
aspersion, sorbitol, manitol y cualquier derivado de celulosa.

025 En ciertas realizaciones, el nücleo de la composición de bromhidrato de bupropion (por
ejemplo, el niicleo de un comprimido XL) puede obtenerse de acuerdo con cualquiera de
los mØtodos descritos en la Patente de los Estados Unidos No. 7.241.805.

En al menos una realizaciOn de la invenciOn, los grÆnulosque se van a comprimir para
30 formar el niicleo del comprimido XL de bromhidrato de brupropion de la invención
descrito aqul, se fabrican mediante el proceso de granulaciOn hómeda. La granulaciOn
hUmeda implica la agitaciOn de un polvo (el fÆrmaco activo) por convenciOn enpresencia
de un liquido (la solución aglutinante) seguida de secado. Para formar los grÆnulos, que
al final se van a comprimir en forma de nüeleos de los comprimidos, primero se granula
35 la sal bromhidrato de bupropion, por ejemplo, con una soluciOn aglutinante, en un
granulador, por ejemplo usando un granulador de lecho fluidizado (por ejemplo, un granulador de lecho fluidizado fabricado por Glatt (Alemania) o Aeromatic (Suiza)). El

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aglutinante (por ej emplo, alcohol polivinilico) se disuelve o se dispersa primero en un disoivente adecuado (por ejemplo, agua). Luego se pulveriza en la parte superior la soiución agiutinante sobre el fÆrmacoen un granulador (por ejemplo, un granulador de
lecho fluidizado). Alternativamente, la granuiación tambiØn se puede lievar a cabo en un mezciador convencional o de alto cizaliamiento. Si fuera necesario, los excipientes
inertes adicionales (por ejemplo, un relleno) se pueden mezclar con la sal bromhidrato de bupropion antes del paso de granulación.

Posteriormente se secan los grÆnulosformados y luego se tamizan antes de mezclar
10 dichos grÆnuloscon el lubricante. En ciertas realizaciones, los grÆnulos secos se tamizan
a travØs de un tamiz de maila de 1,4 mm. Los grÆnulostainizados se mezcian luego con
ci lubricante, y si fuera necesario, con cualquier otro excipiente inerte adicional, que
pueda mejorar ci procesamiento de los comprimidos de liberación extendida de la
invención. La mezcla de los grnu1os con el lubricante y si fuera necesario, con cualquier
15 otro excipiente inerte, como por ejemplo un deslizante, se puede lievar a cabo en un
mezciador en V u otro aparato de mezcla adecuado. Los deslizantes pueden mejorar la capacidad de fluir del polvo. Esto, por ejemplo, puede ser ütii durante la producción de comprimidos a velocidades altas de producción y durante la compactaciOn directa. Sin
embargo, debido a que ci flujo adecuado requerido es un flujo alto, a menudo tambiØn se
20 agrega un deslizante a la granuiacion antes de la formaciOn de comprimidos.
Posteriormente los grÆnuios mezcladosse comprimen en forma de comprimidos y de aqul
en adelante se denominan nücleos de los comprimidos. Los micleos de los comprimidos
se pueden obtener mediante ci uso de tºcnicas y equipos corrientes bien conocidos por los StØcnicos con experiencia. Por ejemplo, los nücieos de los comprimidos XL se pueden
25 obtener con una compresora rotatoria (tambiØn denominada compresora multiestación)
equipada con punzones adecuados.

Los granulos tambiØn se pueden preparar usando otros procesos conocidos por los
tØcnicos con experiencia. Los ej emplos de otros procesos de fabricación de grÆnuios
30 inciuyen granulaciOn seca (por ejemplo, aglutinación, compactación con rodillos),
compresión directa, extrusion, esferonización, granulación por fusion y granuiación

rotatoria.

Un ejemplo del proceso de granulacion para los nücleos XL (iote 60 kg) es ci siguiente:
35 Se usa un procesador de lecho fluidizado para la granulación a fin de agiomerar las
partleulas de los materiales para obtener un tamafio de particula uniforme para la mezcia final. La soluciOn de granulaciOn se prepara por disoiución del agiutinante (por ejemplo,

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alcohol polivinflico) en agua purificada caliente mientras se mezcla. Se puede ajustar el contenido porcentual de sOlidos para obtener una viscosidad que permita controlar la acumulación (tamafio de aglomeración) del material. Una viscosidad menor conduce a particulas mÆs pequefiasy una viscosidad mayor conduce a particulas mÆsgrandes.
5 AdemÆsla velocidad de aplicación (por ejemplo, de aproximadamente 150 g/min a
aproximadamente 250 g/min, incluidos todos los valores y rangos intermedios; o 200
g/min), la posición de la pistola de pulverización (por ejemplo, en la posición central) y ci tamaflo de la boquilla (por ejemplo, de aproximadamente 0,5 mm a aproximadamente 2
mm, incluidos todos los valores y rangos intermedios; o aproximadamente 1 mm) y la
10 presión de pulverización (por ejemplo, de 20 psi a aproximadamente 40 psi, incluidos
todos los valores y rangos intermedios; o aproximadamente 30 psi) contribuyen adicionalmente a controlar el tamafio de partleula. El material activo se fluidiza y
calienta (por ejemplo, de aproximadamente 35°C a aproximadamente 45°C, incluidos
todos los valores y rangos intermedios; o aproximadamente 40°C) antes de comenzar a
15 aplicar la solución. Durante el ciclo de pulverización, la temperatura del lecho (por
ejemplo, de aproximadamente 35°C a aproximadamente 45°C, incluidos todos los valores
y rangos intermedios; o aproximadamente 40°C) se mantiene constante para evitar la humectación en exceso. Una vez que se aplica toda la soiución aglutinante necesaria, el material se seca adicionalmente hasta el valor de LOD (es decir, pØrdida por secado)
20 buscado (por ejemplo, por debajo de aproximadamente 1%) antes de la descarga. La
cantidad de aglutinante (por ejemplo, alcohol polivinIlico) es de aproximadamente 2% a aproximadamente 6%, incluidos todos los valores y rangos intermedios, por ejemplo, aproximadamente 3%; y la concentración de la solución es de aproximadamente 3% a aproximadamente 7%, incluidos todos los valores y rangos intermedios, por ejemplo,
1025 aproximadamente 4,5%. El tiempo del proceso de aglomeración para el lote de 60 kg es
entre aproximadamente 45 minutos y aproximadamente 220 minutos, incluidos todos los
valores y rangos intermedios, por ejemplo, aproximadamente 150 minutos. Una vez que
ci granulado estÆ seco, ci material sepasa a travØs de un tamiz de 1,4 y 2,00 nun para
separar todas las particulas de mayor tamafio. Las particulas de mayor tamaæo se pasan
30 por ci molino para reducirlas. Las particulas de mayor tamano generalmente no estÆn
presentes en un tamaæo que exeeda aproximadamente el 5% de la producción total. Los materiales tamizados y molidos se colocan en un mezclador de cilindros (por ejemplo, un mezclador en V 0 Ufl mezclador de tolva) y se agrega el lubricante (por ejemplo, behenato
de glicerilo). El lubricante se tamiza y se agrega a los grÆnulosy se mezcla al nómero
35 predeterminado de revoluciones o tiempo (por ejemplo, tiempo de mezcla de
aproximadamente 5 mill a aproximadamente 15 mm, incluidos todos los valores y rangos intermedios, por ejemplo, incluidos aproximadamente 10 mm). El porcentaje de

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lubricante se encuentra entre aproximadamente 0,5% y aproximadamente 4%, incluidos todos los valores y rangos intermedios (por ejemplo, incluido aproximadamente 2%). El nivel de lubricación se establece para una cobertura suficiente de la distribución de
tamaflo de partfcula ya sea mÆs grande omÆs pequefia. Otras caracteristicasincluyen la
5 densidad aparente (por ejemplo, de aproximadamente 0,3 g/ml a aproximadamente 0,8
g/ml, incluidos todos los valores y rangos intermedios, por ejemplo, ineluido aproximadamente 0,5 g/ml), y el contenido de humedad (por ejemplo, no mÆsde aproximadamente 1%). El tamaulo de particula y el flujo de la mezcla final son factores
para obtener un lienado uniforme de las cavidades en una compresora rotatoria. El flujo
10 y la velocidad de rotación maxima de la compresora se ajustan (dependiendo del
tipo/tamaflo de la compresora) de modo de no poner en peligro la uniformidad de peso de
los comprimidos individuales. La mezcla del producto Se pasa a travØs de un embudo a
. un dispositivo distribuidor para ilenar las cavidades de la matriz que pasan por debajo de
dicho dispositivo. Se hacen ajustes de peso para mantener el peso dentro del rango
15 especificado, y se hacen ajustes a la regulaciOn de la presión para obtener la dureza
necesaria. Algunos componentes de los comprimidos que se controlan son el espesor y la friabilidad (por ejemplo, menos de aproximadamente 0,5%) del comprimido. Un espesor adecuado (con relación al area superficial total) y una menor friabilidad ayudan a reducir
ci daub del nücleo y la pØrdida de principio activo durante ci recubrimiento. Se toman
20 muestras de los comprimido a intervalos predeterminados para controlar las
especificaciones.

Recubrimientos

’ Los nücleos de los comprimidos se pueden recubrir para la administración a un sujeto.
25 En al menos una realización de la invenciOn, los nücleos de los comprimidos se recubren
con un recubrimiento de liberaciOn controlada ("Recubrimiento de liberación controlada
XL") que puede proporcionar una liberación extendida de la sal bromhidrato de
bupropion o mezcla de la sal bromhidrato de bupropion y otro fÆrmaco. En almenos otra realización, los m’ieleos de los comprimidos se recubren con un recubrimiento acuoso de
30 liberación controlada. que comprende una dispersion acuosa de un copoilmero de ester
neutro sin ningün grupo funcional ("Recubrimiento de liberación controlada AQ").

En ciertas realizaciones la forma farmacØutica comprimido comprende una barrera contra
la humedad opcional ademÆsdel recubrimiento de iiberación controlada. El
35 recubrimiento de liberación controlada y la barrera contra la humedad se pueden aplicar
en dos etapas. El recubrimiento de iiberación controlada se puede aplicar directamente
sobre la superficie de los nücleos de los comprimidos y acta controlando la liberación de

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la sal brornhidrato de bupropion. La barrera contra la humedad se puede aplicar directamente sobre la superficie del recubrimiento de liberación controlada para impedir
o retrasar la absorción de humedad.

5 A continuación se proporcionan ejemplos profØticos de las formulaciones del
recubrimiento de liberación controlada. Se debe entender que los constituyentes y/o las proporciones de los constituyentes en estos recubrimientos asI como las cantidades de
Østos se pueden variar para lograr formulaciones que posean diferentes caracterIsticas de liberación. En todos los casos en los que se proporcionan ejemplos profØticos estas
10 composiciones estÆn destinadas a serejemplos y se debe comprender que los
procedimientos, los constituyentes, sus cantidades y similares especIficos, se pueden
variar para obtener una eomposición que posea las propiedades deseadas

En al menos una realización, el recubrimiento de liberación controlada es una
15 formulaciOn de recubrimiento que proporciona una liberación retardada del o los
fÆrmacosactivos desde el nücleo del comprimido. En dichas realizaciones, la formulación de recubrimiento a aplicarse al nücleo puede comprender:
EUDRAGITfi L12.5 aproximadamente 50% en peso de la suspension de
recubrimiento

20 Citrato de trietilo aproximadamente 0,63% en peso de la suspensiOn de
recubrimiento

Talco aproximadamente 1,25% en peso de la suspension de
recubrimiento

Alcohol isopropIlico aproximadamente 48,12% en peso de la suspension de
025 recubrimiento
Total de sólidos = aproximadamente 8,1%
Contenido del polImero de la suspensiOn = aproximadamente 6,3%

En ciertas realizaciones, el recubrimiento de liberación controlada de la forma
30 fannaeØutica de bromhidrato de bupropion (por ej emplo, ci recubrimiento de liberación
controlada de un comprimido XL) puede obtenerse de acuerdo con cuaiquiera de los mØtodos descritos en la presente.

La preparación de la formulaciOn de recubrimiento de iiberaciOn controlada de dichas
35 realizaciones (por ej emplo, recubrimiento de liberación controlada que puede
proporcionar una liberación retardada del fªrmaco activo) puede ser la siguiente: talco y citrato de trietilo se homogenizan en ci disolvente mediante un homogenizador durante

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aproximadamente 10 minutos. La suspension se vierte directamente en la dispersiOn de EUDRAGITfi L12.5 y se agita suavemente para evitar la sedimentaciOn. El recubrimiento se pulveriza sobre los comprimidos hasta que se hayan aplicado aproximadamente 5 mg/cm2 de EUDRAGITfi L al nücleo del comprimido.

En al menos una realizaciOn, el recubrimiento de liberación controlada puede
proporcionar una liberaeión sostenida del fÆrmaco activo desde elniicleo del
comprimido. La formulación del comprimido puede comprender:
EUDRAGITfi RL 12.5 aproximadamente 10% en peso de la suspension de
10 recubrimiento
EUDRAGITfi RS 12.5 aproximadamente 30% en peso de la suspension de recubrimiento

Sebacato de dibutilo aproximadamente 0,5% en peso de la suspensiOn de
recubrimiento

15 Talco aproximadamente 3,5g en peso de la suspension de
recubrimiento

Estearato de magnesio aproximadamente 1% en peso de la suspensiOn de
recubrimiento

Acetona aproximadamente 27,5% en peso de la suspensiOn de
20 recubrimiento

Alcohol isopropflico aproximadamente 27,5% en peso de la suspension de
recubrimiento,
Total de sOlidos = aproximadamente 10%

.

Contenido del polimero de la suspensiOn = aproximadamente 5%

25

La preparaciOn de la formulación de recubrimiento de liberación controlada de dichas realizaciones (es decir, liberación controlada que puede proporcionar una liberaciOn
sostenida del fÆrmacoactivo) puede 5cr la siguiente: Se mezclan el sebacato de dibutilo,
el talco y el estearato de magnesio y se dispersan finamente junto con los diluyentes
30 acetona y alcohol isopropilico. La suspensiOn se combina luego con las dispersiones de
polimero EUDRAGITfi. El recubrimiento se pulveriza sobre el ncleo hasta que se
hayan aplicado aproximadamente 10 mg/cm2 del polimero al nücleo.

En al menos una realización, el recubrimiento de liberaciOn controlada es un
35 recubrimiento mezcla de pollmeros que posee polimero dependiente del pH (por ejemplo,
EUDRAGITfi L30D55) en combinaciOn con un polimero de liberaciOn sostenida (por ejemplo, AQUACOATfi). Dicha formulación de recubrimiento puede comprender:

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AQUACOATfi (etilcelulosa 30%) suspension de recubrimiento
EUDRAGITfi L30 D 55
suspension de recubrimiento
5 Citrato de trietilo

10

15

20

 25

30

suspension de recubrimiento
Agua
suspension de recubrimiento

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aproximadamente 21% en peso de la

aproximadamente 21% en peso de la

aproximadamente 3% en peso de la

aproximadamente 55% en peso de la

Total de sólidos = aproximadamente 15,6%
Contenido del poilmero de la suspension = aproximadamente 12,6%

La aplicaciOn del recubrimiento mezcla de poilmeros puede ser la siguiente: Recubrimiento aplicado a una aplicación de 10 mg/cm2 de poilmero al nücleo de fÆrmaco.

En al menos una realización, el recubrimiento de liberación controlada es un fÆrmacoque contiene al menos otro fÆrmaco(por ej emplo, Citalopram) encirna de un nücleo que contiene sal bromhidrato de bupropion. La formulaciOn de recubrimiento puede comprender:
KOLLIDONfi VA64 aproximadamente 2,5% en peso de la suspensiOn de recubrimiento de fÆrmaco

(CopolImero de vinilpirrolidona-acetato de vinilo)
KLUCELTMEF aproximadamente 2,5% en peso de la suspension de recubrimiento de fÆrmaco
(Hidroxipropilcelulosa)
Citalopram. aproximadamente 2% en peso de la suspension de
recubrimiento de fÆrmaco
Talco aproximadamente 3% en peso de la suspension de
recubrimiento de fÆrmaco

2-propanol aproximadamente 90% en peso de la suspension de
recubrimiento de frmaco
Total de sOlidos = aproximadamente 10%
Contenido del poilmero de la suspensiOn = aproximadamente 5%

35 La aplicación de la formulaciOn de recubrimiento de fÆrmacopuede ser la siguiente: El recubrimiento de fÆrmacose pulveriza sobre los comprimidos hasta que se haya aplicado
la cantidad deseada de otro fÆrmaco (por ejemplo, Citalopram).

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Posteriormente se puede aplicar una capa protectora como un recubrimiento cosmØtico y tambiØn para prevenir la adhesion del comprimido.
La formulación de la capa protectora que se aplica al nücleo recubierto de f.rmaco puede comprender:
5 KOLLIDONfi VA64 aproximadamente 2,5% en peso de la suspensiOn de capa
protectora
(Copoilmero de vinilpirrolidona-acetato de vinilo)
KLUCELTMEF aproximadamente 2,5% en peso de la suspensiOn de
capa protectora
10 (Hidroxipropilcelulosa)
Talco aproximadamente 2,5% en peso de la suspension de capa
protectora
Alcohol isopropilico aproximadamente 92,5% en peso de la suspension de capa
W protectora
15 Total de sólidos = aproximadamente 7,5%
Contenido del polImero de la suspension = aproximadamente 5%

La aplicaciOn de la formulación de la capa de protecciOn puede ser la siguiente: La capa
se aplica hasta un aurnento de peso de aproximadamente 2% (expresado cono % del
20 nücleo de comprimido recubierto de fÆrrnaco).

El recubrimiento de liberaciOn controlada de liberaciOn extendida (XL)
El recubrimiento de liberaciOn controlada XL es un recubrimiento semipermeable que

10 comprende un polImero formador de pelicula, insoluble en agua y permeable al agua, un
25 polimero soluble en agua y opcionalmente wi plastificante.

Los ejemplos no limitantes de los pollmeros formadores de pelicula, insolubles en agua y permeable al agua ütiles para el recubrimiento de liberación controlada XL incluyen
Øteres de celulosa, Østeres de celulosa, alcohol polivinIlico y sus mezclas. En ciertas
30 realizaciones, los polimeros formadores de pelicula, insolubles en agua y permeables al
agua pueden ser las etil celulosas y se pueden seleccionar entre los siguientes ejemplos no limitantes: etilcelulosa grados PRIM, PR45, PR20, PR10 y PR7 (ETHOCELfi, Dow), y cualquier combinaciOn de ellos. En al menos una realización de la invención, la
etilcelulosa de grado PR100 es el poilmero formador de pelicula, insoluble en agua y
35 permeable al agua. En ciertas realizaciones, la cantidad de poilmero formador de pelicula
insoluble en agua y permeable al agua puede variar de aproximadamente 1% a aproximadamente 12% en peso del peso seco del comprimido, ineluidos todos los valores

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y rangos intermedios. Por ejernplo, en ciertas realizaciones la cantidad de poilmero formador de pelicula, insoluble en agua y permeable al agua estÆ presente en una
cantidad de aproximadamente 5% a aproximadamente 10% y en otras realizaciones de aproximadamente 6% a aproximadamente 8% en peso del peso seco del comprimido. En
5 ciertas realizaciones de los comprimidos de liberación modificada de 174 mg de dosis de
la invenciOn, la cantidad de poilmero formador de pelicula insoluble en agua y permeable
al agua es de aproximadamente 3% a aproximadamente 8% en peso del peso seco del comprimido, preferiblemente de aproximadamente 6% a aproximadamente 7% en peso
del peso seco del comprimido, incluidos todos los valores y rangos intermedios. En lo
10 que se refiere al recubrimiento de iiberación controlada, la cantidad de poilmero
formador de pelicula, insoluble en agua y permeable al agua en ciertas realizaciones del comprimido de 174 mg de dosis puede ser de aproximadamente 35% a aproximadamente 60% en peso del peso seco del recubrimiento de liberación controlada, incluidos todos los valores y rangos intermedios, y en ciertas realizaciones de aproximadamente 40% a
15 aproximadamente 50% en peso del peso seco del recubrimiento de liberación controlada.
En ciertas realizaciones de los comprimidos de liberación modificada de 348 mg de dosis
de la invención, la cantidad de polImero formador de pelicula, insoluble en agua y
permeable al agua puede ser de aproximadamente 2% a aproximadamente 5% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios, y en otras
20 realizaciones de aproximadamente 3% a aproximadamente 4% en peso del peso seco del
comprimido. En lo que se refiere al recubrimiento de liberación controlada en sí, ci
polImero formador de pelicula, insoluble en agua y permeable al agua en ciertas
realizaciones de los comprimidos de 348 mg de dosis estÆ presente en una cantidad de aproximadamente 40% en peso del peso seco del recubrimiento de liberación controlada.
 25 En ciertas realizaciones de los comprimidos de liberación modificada de 522 mg de dosis
de la invención, la cantidad de polimero formador de pelicula, insoluble en agua y
permeable al agua puede ser de aproximadamente 0,5% a aproximadamente 10% en peso
del peso seco del comprimido, incluidos todos los valores y rangos intermedios, y en
otras realizaciones de aproximadamente 1% a aproximadamente 6% en peso del peso
30 seco del comprimido. En lo que se refiere al recubrimiento de liberación controlada en sí,
el polImero formador de pelicula, insoluble en agua y permeable al agua en ciertas realizaciones de los comprimidos de 522 mg de dosis estÆ presente en una cantidad de aproximadamente 37% en peso del peso seco del recubrimiento de liberaeiOn controlada.

35 Los ejemplos no limitantes de polImeros solubles en agua ütiles para ci recubrimiento de
liberación controlada XL incluyen polivinilpirrolidona, hidroxipropilmetilcelulosa, hidroxipropilcelulosa y sus mezclas. En a! menos una realización ci polImero soluble en

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agua es polivinilpirrolidona (POVIDONEfi USP). La cantidad de polimero soluble en agua puede variar de aproximadamente 1,5% a aproximadamente 10% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, la cantidad de polimero soluble en agua es de aproximadamente 3%
5 a aproximadamente 8% y en otras realizaciones de aproximadamente 4% en peso del
peso seco del comprimido. En Jo que se refiere al recubrimiento de liberación controlada
en sí, en ciertas realizaciones la cantidad de polimero soluble en agua presente es de aproximadamente 25% a aproximadamente 55% en peso del peso seco del recubrimiento
de liberación controlada, incluidos todos los valores y rangos intermedios. Para ciertas
10 realizaciones de los comprimidos de liberaciOn extendida de 174 mg de dosis de la
invenciOn, la cantidad de polimero soluble en agua es de aproximadamente 3% a aproximadamente 5% en peso del peso seco del comprimido, incluidos todos los valores
y rangos intermedios, y de aproximadamente 25% a aproximadamente 50% en peso del
peso seco del recubrimiento de liberación controlada, incluidos todos los valores y rangos
15 intermedios. Para ciertas realizaciones de los comprimidos de liberaeión extendida de
348 mg de dosis de la invención, la cantidad de polimero soluble en agua presente es de aproximadamente 2% a aproximadamente 5% del peso seco del comprimido, incluidos
todos los valores y rangos intermedios, y de aproximadamente 40% a aproximadamente
50% en peso del peso seco del recubrimiento de liberaciOn controlada, incluidos todos los
20 valores y rangos intermedios. Para ciertas realizaciones de los comprimidos de liberación
extendida de 522 mg de dosis de la invención, la cantidad de polimero soluble en agua
presente es de aproximadamente 2% a aproximadamente 5% del peso seco del
comprimido, incluidos todos los valores y rangos intermedios, y de aproximadamente
. 40% a aproximadamente 50% en peso del peso seco del recubrimiento de liberación
25 controlada, incluidos todos. los valores y rangos intermedios.

En ciertas realizaciones, el recubrimiento de liberaciOn controlada XL comprende,
ademÆs, un plastificante. El uso de plastificantes es opcional, y se pueden agregar a las formulaciones de pelicula de recubrimiento para modificar las propiedades fIsicas de un
30 polimero para hacerlo mÆs utilizable durante lafabricación. Los plastificantes pueden ser
disolventes orgÆnicos de alto puntode ebullición usados para impartir flexibilidad a materiales polimØricos de otro modo duros o quebradizos. Los plastificantes causan en general una reducción en las fuerzas intermoleculares cohesivas a lo largo de las cadenas
del polimero que dan lugar.a diversos cambios en las propiedades del polimero incluidas
35 una reducciOn de la resistencia a!a tension y un aumento de la elongacion y una
reducción de la temperatura de transiciOn vItrea o la temperatura de ablandamiento del polimero. La cantidad y la elecciOn del plastificante pueden afectar a la dureza de un

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comprimido e inciuso pueden afectar a sus caracteristicas de disoluciOn o de
desintegración, asi como a su estabilidad fIsica y qulmica. Ciertos plastificantes pueden
aumentar la elasticidad y/o flexibilidad de un recubrimiento, reduciendo de ese modo su fragilidad. Una vez que se fabrica la forma farmacØutica, ciertos plastificantes pueden
5 actuar aumentando la hidrofihicidad de o de los recubrimientos y/o del nücleo de la forma
farmacØutica en ci ambiente de uso (in vitro o in vivo). Los ejemplos no limitantes de plastificantes que se pueden usar en ci recubrimiento de liberación controlada descrito
aquf, incluyen monoglicØridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina;
10 propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicØrido de
acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de coiza, aceite de oliva, aceite de sØsamo, citrato de trietilo; alcoholes polihIdricos, glicerol, glicerina,
sorbitol, Østeres de acetato, triacetato de glicerol, acetil trietil citrato, ftalato de dibencilo, ftalato de dihexilo, octil ftalato de butilo, ftalato de di isononiio, octil ftalato de butilo,
15 azelato de dioctilo, taiato epoxidado, trimelitato de triisoctilo, ftalato de dietilhexilo,
ftalato de di-n-octilo, ftalato de di-i-octilo, ftalato de di-i-deciio, ftalato de di-n-undecilo, ftalato de di-n-tridecilo, trimeiitato de tri-2-etilhexilo, adipato de di-2-etilhexilo, sebacato
de di-2-etilhexiio, azeiato de di-2-etilhexiio, sebacato de dibutilo, oxalato de dietilo,
maiato de dietilo, fumarato de dietilo, suceinato de dibutilo, malonato de dietilo, ftalato
20 de dibutilo, sebacato de dibutilo, tributirato de glicerol, polioles (por ejempio,
polietilenglicoi) de diversos pesos moleculares y sus mezclas. EstÆ contempladoy dentro
del alcance de la invención, que se puede usar una combinación de plastificantes en la
presente formulación. En al menos una realizaciOn de la invención, ci plastificante es polietilenglicol 4000, sebacato de dibutilo o sus mezcias. La cantidad de plastificante
025 para ci recubrimiento de liberación controlada puede variar en una cantidad entre
aproximadamente 0,5% y aproximadamente 4% en peso del peso seco del comprimido,
inciuidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci plastificante estÆpresente en una cantidad entre aproximadamente 2% y
aproximadamente 3% en peso del peso seco del comprimido. Para ciertas realizaciones
30 de los comprimidos de iiberación extendida de 174 mg de dosis de la invención, la
cantidad de plastificante presente en ci recubrimiento de liberaciOn controlada es de aproximadamente 1% a aproximadamente 4% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios. Para ciertas realizaciones de los comprimidos de iiberación extendida de 348 mg de dosis de la invención, la cantidad de
35 plastificante presente es de aproximadamente 0,5% a aproximadamente 4% en peso del
peso seco del comprimido, incluidos todos los valores y rangos intermedios. Para ciertas realizaciones de los comprimidos de liberación extendida de 522 mg de dosis de la

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invención, la cantidad de plastificante presente es de aproximadamente 0,5% a aproximadamente 4% en peso del peso seco del comprimido, incluidos todos los valores
y rangos intermedios. En ciertas realizaciones de las formas farmacØuticas de 174 mg,
348 mg y 522 mg, el plastificante estÆ presenteen una cantidad entre aproximadamente
5 6% y aproximadamente 30% en peso del peso seco del recubrimiento de liberación
controlada. Por ejemplo, en ciertas realizaciones ci plastificante estª presente en una cantidad de aproximadamente 12% en peso del peso seco del recubrimiento de liberación controlada.

10 La relación pollmero formador de pelicula, insoluble en agua y permeable al
agua:plastificante:polimero soluble en agua para el recubrimiento de liberaciOn
controlada XL de ciertas realizaciones de la invención descritas en la presente puede

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variar de aproximadamente 3:1:4 a aproximadarnente 5:1:2, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, la relación poilmero formador
15 de pelicula, insoluble en agua y permeable al agua:plastificante:polimero soluble en agua
para el recubrimiento de liberación controlada XL es de aproximadamente 4:1:3. Para
otras realizaciones del comprimido XL, la relación pollmero formador de pelicula,
insoluble en agua y permeable al agua:plastificante:polimero soluble en agua para el recubrimiento de liberación controlada XL es de aproximadamente 7:2:6 a
20 aproximadamente 19:5:18, incluidos todos los valores y rangos intermedios. En al menos
una realización, la relación pollmero formador de pelicula, insoluble en agua y permeable
al agua:plastificante:polimero soluble en agua para el recubrimiento de liberaciOn
controlada XL es de aproximadamente 13:4:12. En al menos una realización de la forma
. farmacØutica de 522 mg, la relación poilmero formador de pelicula, insoluble en agua y
25 permeable al agua:plastificante:polimero soluble en agua para el recubrimiento de
liberación controlada XL es de aproximadamente 13:6:16.

En ciertas realizaciones, ci recubrimiento de liberación controlada XL del comprimido de bromhidrato de bupropion puede obtenerse de acuerdo con cualquiera de los mØtodos
30 descritos en la presente.

La preparación y aplicación del recubrimiento de liberación controlada XL pueden ser las siguientes. El polimero formador de pelicula insoluble en agua y permeable a! agua (por ejemplo, etiicelulosa) y el plastificante (por ejemplo, polietiienglicol 4000), se disuelven
35 en un disolvente orgÆnico(por ejemplo, una mezcla de alcohol etIlico). En la fabricaciOn
de realizaciones que no requieren un plastificante, ci poilmero formador de pelicula, insoluble en agua y permeable al agua se puede disolver en ci disolvente organico sin ci

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plastificante. A continuación se agrega el polImero soluble en agua (por ejemplo, polivinilpirrolidona) hasta que se logra una mezcla homogØnea. DespuØs Se pulveriza la solución de recubrimiento de liberaciOn controlada resultante sobre los nücleos de los comprimidos usando uæ equipo de lecho fluidizado revestidor de comprimidos o
5 cualquier otro equipo de revestimiento adecuado conocido por los tØenicos en la materia,
hasta que se logra ci aumento de peso deseado. Posteriormente se secan los nücleos de
los comprimidos recubiertos con ci recubrimiento de liberaciOn controlada. En la fabricación de las realizaciones que tienen una barrera contra la humedad, ci
recubrimiento de liberación controlada se seca antes de aplicar la barrera contra la
10 humedad.

Un ejemplo del proceso de recubrimiento para el recubrimiento de liberación controlada
XL es el siguiente: La solución de recubrimiento de liberación controlada XL se prepara disolviendo el poilmero insoluble en agua (por ejemplo, etilcelulosa) y ci poilmero
15 soluble en agua (por ejemplo, polivinilpirrolidona) y una mezcla de alcohol etIlico
mientras se mezcla y se sigue con el agregado del o de los plastificantes (por ejemplo,
mezcla de polietilenglicol 4000 y sebacato de dibutilo). Una vez disueltos
completamente, la solución se homogeneiza para obtener una mezcla uniforme de
viscosidad apropiada. Este procedimiento ayuda a obtener una mezcla complej a de una
20 pelIcula permeable al agua para controlar la liberaeión del fÆrmacoactivo. La
composición de la solución se puede formular de modo que contenga diversos niveles del poilmero insoluble en agua y del poilmero soluble en agua y una mezcla del o de los plastificantes. La función de liberación se controla ademÆs mediante ciespesor de Ia
peilcula aplicada y se mide como un aumento del peso de los sólidos en ci recubrimiento
025 requerido. Los comprimidos se recubren en una paila de recubrimiento con control de la
velocidad de la paila (por ejemplo, de aproximadamente 8 rpm a aproximadamente 14
rpm, incluidos todos los valores y rangos intermedios, y en algunos casos de aproximadamente 12 rpm), la velocidad de pulverización (por ejemplo, de
aproximadamente 150 g/min a aproximadamente 250 g/min, incluidos todos los valores y
30 rangos intermedios, y en algunos casos de aproximadamente 200 g/min), la presión de
pulverización (por ejemplo, de aproximadamente 15 psi a aproximadamente 25 psi,
incluidos todos los valores y rangos intermedios, y en algunos casos de aproximadamente
20 psi), ci volumen de suministro (de aproximadamente 800 a aproximadamente 1.000
pies cübicos/min, incluidos todos los valores y rangos intermedios, y en algunos casos de
35 aproximadamente 900 pies cübicos/min) y la temperatura del aire (por ejemplo, de
aproximadamente 50°C a aproximadamente 60°C, incluidos todos los valores y rangos intermedios, y en algunos casos de aproximadamente 55°C), controladas mediante una

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temperatura del lecho y/o una temperatura de salida de aproximadamente 38°C a aproximadamente 42°C, incluidos todos los valores y rangos intermedios, y en algunos
casos de aproximadamente 40°C. Al finalizar el ciclo de recubrimiento, los comprimidos
se secan y Se descargan en envases a granel. El proceso de impresiOn comprende la transferencia de una irnagen de impresión desde una placa de impresión cubierta con tinta negra comestible y transferida mediante un rollo o almohadilla de irnpresión sobre la superficie de los comprimidos. Los comprimidos impresos se transfieren a travØs de un elemento de secado antes de descargarlos en los envases a granel. Las muestras para la prueba final se toman durante todo el proceso de impresión.

El tØcnico con experiencia apreciarÆ que el control de la permeabilidad puede controlar la liberaciôn de la sal bromhidrato de bupropion y/o la cantidad de recubrimiento aplicada a
los nücleos de los comprimidos. La permeabilidad del recubrimiento de liberación
controlada XL, se puede alterar variando la relación poilmero formador de pelIcula,
15 insoluble en agua y permeable al agua:plastificante:polfmero soluble en agua y/o la
cantidad de recubrimiento aplicada al nücleo del comprimido. Se puede obtener una
liberación mas extendida con una cantidad mayor de poilmero formador de pelIcula
insoluble en agua y permeable al agua. La adición de otros excipientes al nücleo del comprimido tambiØn puede alterar la permeabilidad del recubrimiento de liberación
20 controlada. Por ejemplo, si se desea que el nücleo del comprimido contenga ademÆs un
agente de expansiOn, se puede aumentar la cantidad de plastificante en el recubrimiento
de liberación controlada para hacer el recubrimiento mÆs flexible, puestoque la presión
ejercida por el agØnte de expansion en un recubrimiento menos flexible podria romper el recubrimiento. AdemÆs, la proporciOn de poilmero formador de pelicula,insoluble en

W25 agua y permeable al agua y de polImero soluble en agua, tambiØn Se puede alterar
dependiendo de si SC desea una disolución y/o un perfil de liberaciOn mÆsrÆpidoso mÆs
lentos.

Dependiendo de la disoluciOn o del perfil de Iiberación in vivo deseados, el aumento del
30 peso despuØs de recubrir el nücleo del comprimido con ci recubrimiento de liberación
controlada XL puede variar tipicamente de aproximadamente 3% a aproximadamente
30% del peso del nücleo del comprimido seco, incluidos todos los valores y tangos intermedios. Para tin comprimido de liberación extendida de 174 mg de dosis de acuerdo
con ciertas realizaciones, el aumento de peso puede variar tfpicamente de
35 aproximadamente 10% a aproximadamente 17% del peso del nücleo del comprimido
seco, incluidos todos los valores y rangos intermedios. Para ci comprimido de liberación extendida de 348 mg de dosis de ciertas realizaciones, el aumento de peso puede variar de

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aproximadamente 7% a aproximadamente 10% del peso del nücleo del comprimido seco, incluidos todos los valores y rangos intermedios. Para el comprimido de liberaciOn extendida de 522 mg de dosis de ciertas realizaciones, el aumento de peso puede variar de aproximadamente 5% a aproximadamente 15% del peso del nücleo del comprimido seco,
5 incluidos todos los valores y rangos intermedios.

Recubrimiento de liberación controlada AQ
El recubrimiento de liberación controlada AQ es un recubrimiento de liberaeión
controlada monoiltico estable que comprende una dispersion acuosa de un copoilmero de
10 un ester neutro sin ningün grupo funcional, un poliglicol con un punto de fusion mayor a
aproximadamente 55°C y uno o mÆsexcipientes farmacØuticamente aceptables; donde
dicha composición de recubrimiento se aplica sobre la forma farrnaeØutica y se cura a una temperatura al menos igual o mayor que el punto de fusion del poliglicol. La
formulaciOn de recubrimiento es muy versÆtilporque se puede usar para recubrir una
15 diversidad de nücleos de fÆrmacoy se puede manipular fªcilrnente para obtener ci perfil
de liberación del fÆrmaco deseado.

En ciertas otras realizaciones, ci recubrimiento de liberaciOn controlada AQ comprende
una dispersion acuosa de una etilcelulosa, un poliglicol con un punto de fusiOn mayor a
20 aproximadamente 55°C y uno o mÆsexcipientes farmacØuticamente aceptables; donde
dicha composición de recubrimiento se aplica sobre la forma farmacØutica y se cura a una temperatura al menos igual o mayor que ci punto de fusiOn del poliglicol. Ejemplos no limitantes de dispersiones acuosas de una etilcelulosa incluyen SURELEASEfi
(Colorcon, Inc., West Point, Pa., EE. UU.) y AQUACOATfi (FMC Corp., Filadelfia, Pa.,
5 EE. UU.). Las combinaciones son factibies.

En ciertas realizaciones, ci recubrimiento de liberación controlada AQ es un
recubrimiento monolitico de iiberación controlada estable que se forma mediante un
proceso que comprende recubrir el nücleo con una composición de recubrimiento para
30 formar un nócieo recubierto con un recubrimiento intermedio, y curar ci nücleo
recubierto para fonnar un recubrimiento de liberación controlada AQ. En al menos una realización, la composiciOn de recubrimiento comprende una dispersion acuosa de un copoilmero de un ester neutro sin ningün grupo funcional, un poliglicol con un punto de fusion de al menos 55°C y uno o mÆs excipientesfarmacCuticamente aceptables. El
35 curado se lieva a cabo a una temperatura al menos igual o mayor que ci punto de fusion
del poliglicol. En at menos una realización, ci recubrimiento de iiberación controlada
AQ estable comprende una dispersion acuosa de tin copoilmero de un ester neutro sin
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ningn grupo funcional, un poliglicol con un punto de fusion de al menos 55°C y uno o
mÆs excipientes farmacØuticamenteaceptables.

La dispersion acuosa de un copolimero de un ester neutro sin ningün grupo funcional
5 puede ser una dispersion de copolimero de acrilato de etilo y metacrilato de metilo.
Ejemplos no limitantes de dispersiones de copolimero de acrilato de etilo y metacrilato de metilo incluyen una dispersion acuosa al 30% de un copolimero neutro basado en acrilato
de etilo y metacrilato de metilo (por ejemplo, EUDRAGITfi NE30D), una dispersiOn
acuosa a! 40% de an copolimero neutro basado en acrilato de etilo y metacrilato de
10 metilo (por ejemplo, EUDRAGITfi NE40D), EUDRAGITfi NM30D, KOLLICOATfi
EMM30D y sus combinaciones. En al menos una realizaciOn, el copolimero de un ester neutro sin ning1n grupo funcional utilizado en la composición de recubrimiento de
liberaciOn controlada es EUDRAGITfi NE30D, EUDRAGITfi NE40D o sus mezclas. El copolimero de un ester neutro sin ningün grupo funcional puede estar presente en ciertas
15 realizaciones en una cantidad de aproximadamente 1% a aproximadamente 35% en peso
de la eomposiciOn de recubrimiento, incluidos todos los valores y subrangos intermedios, dependiendo del agente terapØuticamente activo utilizado y ci perfil de iiberación
controlada deseado. En ciertas realizaciones, el copolimero de un ester neutro sin ningün grupo funcional estÆ presente en una cantidad deaproximadamente 20% a
20 aproximadamente 99,5% en peso seco del recubrimiento de liberaciOn controlada AQ,
incluidos todos los valores y subrangos intermedios. En otras realizaciones, el
copolimero de un ester neutro sin ningün grupo funcional estÆpresente en una cantidad
de aproximadaniente 25% a aproximadamente 60% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios. En otras
25 realizaciones adicionales, ci copolimero de un ester neutro sin ningün grupo funcional
estÆ presente enuna cantidad de aproximadamente 37% a aproximadamente 50% en peso seco del recubrimiento de liberaciOn controlada AQ, incluidos todos los valores y
subrangos intermedios; por ejemplo, incluidos aproximadamente 38%, aproximadamente 39%, aproximadamente 40%, aproximadamente 41%, aproximadamente 42%,
30 aproximadamente 43%, aproximadamente 44%, aproximadamente 45%,
aproximadamente 46%, aproximadamente 47%, aproximadamente 48% y
aproximadamente 49% en peso seco del recubrimiento de!iberación controlada AQ. En ciertas realizaciones, ci copolimero de un ester neutro sin ningn grupo funcional estÆ presente en la composiciOn del recubrimiento en una cantidad entre aproximadamente
35 0,4% y aproximadamente 39,8% en peso seco del comprimido, incluidos todos los
valores y subrangos intermedios; en otras realizaciones, en una cantidad de aproximadamente 0,8% a aproximadamente 24,0% en peso seco del comprimido,

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incluidos todos los valores y subrangos intermedios; y en otras realizaciones adicionales
en una cantidad de aproximadamente 2,0% a aproximadamente 5,5% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios.

5 TambiØn se pueden incluir agentes hidrófilos en el recubrimiento de liberación controlada
AQ para promover la humectación del recubrimiento cuando estÆen contacto con los lIquidos gastrointestinales. Los ejemplos no limitantes de dichos agentes hidrófilos
incluyen poilmeros hidrófilos solubles en agua como hidroxipropilmetilcelulosa
(HPMC), hidroxipropilcelulosa (HPC) y sus combinaciones. En al menos una
10 realización, la HPMC es el poilmero hidrófiio soluble en agua. Si se van a incluir agentes
hidrófilos en la composieión del recubrimiento, dichos agentes pueden estar presentes en
una cantidad de aproximadamente 0,1% a aproximadamente 10% en peso de la
composición del recubrimiento, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, los agentes hidrófilos estÆn presentes en una cantidad
15 entre aproximadamente 0,1% y aproximadamente 5%, y en otras realizaciones entre
aproximadamente 0,1% y aproximadamente 3% en peso de la composición del recubrimiento de liberación controlada. En ciertas realizaciones, el agente hidrófilo estd presente en una cantidad de mas de aproximadamente 0% a aproximadamente 35% en
peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y
20 subrangos intermedios; prŁferiblemente de aproximadamente 8% aaproximadamente
30% en peso seco del recubrimiento de liberaciOn controlada AQ, incluidos todos los
valores y subrangos intermedios, y mÆs preferiblementede aproximadamente 12% a aproximadamente 26% en peso seco del recubrimiento de liberación controlada AQ,
incluidos todos los valores y subrangos intermedios. En ciertas realizaciones, ci agente
025 hidrOfilo estÆ presenteen la formulaciOn de recubrimiento en una cantidad de mÆsde
aproximadamente 0% a aproximadamente 14,0% en peso seco del comprimido, incluidos
todos los valores y subrangos intermedios; preferiblemente de aproximadamente 0,2% a aproximadamente 6,0% en peso seco del comprimido, incluidos todos los valores y
subrangos intermedios, y mÆspreferiblemente de aproximadamente 0,8% a
30 aproximadamente 2,5% en peso seco del comprimido, incluidos todos los valores y
subrangos intermedios.

La formulación del recubrimiento de liberación controlada AQ tambiØn comprende un poliglicol con un punto de fusion mayor a 55°C. El poliglicol utilizado en el
35 recubrimiento de liberación controlada AQ puede ser un polietilenglicol con un peso
molecular promedio que varia entre aproximadamente 4.000 daltones y aproximadamente 35.000 daltones. Ejemplos no limitantes de un poliglicol con un punto de fusion no

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mayor a 55°C incluyen polietilenglicol 4000, polietilenglicol 4600, polietilenglicol 6000, polietilenglicol 8000, polietilenglicol 10000, polietilenglicol 12000, polietilenglicol
20000, polietilenglicol 35000 y sus mezclas. En ciertas realizaciones, el poliglicol se selecciona del grupo que consiste en polietilenglicol 6000, polietilenglicol 8000,
5 polietilenglicol 10000, polietilenglicol 12000 y sus mezclas. En al menos una
realización, el poliglicol utilizado en la composición de recubrimiento del recubrimiento
de liberación controlada AQ es polietilenglicol 8000. El poliglicol puede estar presente
en ciertas realizaciones en una cantidad de aproxirnadamente 0,1% a aproximadamente
10% en peso de la composiciOn de recubrimiento, incluidos todos los valores y subrangos
10 intermedios. En ciertas realizaciones, el poliglicol estÆpresente en una cantidad de
aproximadamente 0,5% a aproximadamente 28% en peso seco del recubrimiento de
liberación controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones, el poliglicol estÆpresente en una cantidad de aproximadamente 4% a aproximadamente 17% en peso seco del recubrimiento de liberaciOn controlada AQ,
15 incluidos todos los valores y subrangos intermedios. En otras realizaciones adicionales, ci
poliglicol estÆpresente en una cantidad de aproximadamente 7,2% a aproximadamente
15,2% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los
valores y subrangos intermedios. En ciertas realizaciones, el poliglicol estÆpresente en la composición del recubrimiento en una cantidad entre aproximadamente 0,1% y
20 aproximadamente 11,2% peso seco del comprimido, incluidos todos los valores y
subrangos intermedios; en otras realizaciones, en una cantidad de aproximadamente 0,1%
a aproximadamente 8,0% en peso seco del comprimido, incluidos todos los valores y
subrangos intermedios; y en otras realizaciones adicionales en una cantidad de
aproximadamente 0,2% a aproximadamente 2,8% en peso seco del comprimido,
 25 incluidos todos los valores y subrangos intermedios. Otros ejempios de derivadôs
adecuados de poliglicol con un punto de fusion de al menos aproximadamente 55°C
incluyen, pero no exciusivamente, Poloxamer 188, Poloxamer 338, Poloxamer 407,

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ó xidos de polietileno, Øteres aiquilicos de polioxietileno y estearatos de polioxietileno y

sus mezclas.

AdemÆs delos copolfmeros y el poliglicol, el recubrimiento de liberación controlada AQ comprende al menos un excipiente farmacØuticamente aceptabie. Los excipientes pueden incluir, pero no exciusivamente, antiadherentes, emulsionantes, antiespumantes,
saborizantes, colorantes y sus mezclas. Los tØcuicos con experiencia en el tema saben
35 que dependiendo de la función principal a que estÆndestinados los excipientes pueden
afectar a las propiedades del recubrimiento de varias maneras, y por lo tanto se pueden describir muchas sustancias usadas en formulaciones de recubrimiento como

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multifuncionales. Un trabajador capacitado sabrÆ,basado en su conocimiento tØcnico,
quØ excipientes farmacØuticamente aceptables son adecuados para la composición del recubrimiento de liberación controlada AQ deseado.

5 La adherencia de las peilculas polimØricas es un factor para el recubrimiento de las
formas farmacØuticas sólidas y para ci paso de curado posterior (tratamiento tØrmico posterior al recubrimiento). Durante ci recubrimiento con poilmeros celulósicos o
acrIlicos, puede ocurrir a veces una aglomeración no deseada de varios grÆnulos o perlas,
por ejemplo a mayores temperaturas de procesamiento del producto. En consecuencia,
10 puede ser aconsej able la adición de antiadherentes a las formulaciones de recubrimiento
en ciertas realizaciones. Los antiadherentes que se pueden usar en ciertas realizaciones
incluyen, pero no exciusivamente, Æcido adIpico, estearato de magnesio, estearato de
calcio, estearato de cinc, aceites vegetales hidrogenados, esterotex, monoestearato de

IS glicerilo, talco (por ejemplo, talco 400), benzoato de sodio, lauril sulfato de sodio, lauril
15 sulfato de magnesio y sus mezclas. En al menos una realizacióu, ci antiadherente es
talco. El talco tambiØn puede actuar como humectante. Las mezclas de antiadherentes
son factibles. La cantidad de antiadherente en la composición de recubrimiento de
liberación controlada puede variar en una cantidad de aproximadamente 1% a aproximadamente 15% en peso de la composición del recubrimiento de liberación
20 controlada, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas
realizaciones, el antiadherente estÆpresente en una cantidad entre aproximadamente 1% y aproximadamente 7% en peso de la composición de recubrimiento de liberación
controlada. En ciertas realizaciones, ci antiadherente estÆ presenteen una cantidad de mÆs
de aproximadamente 0% a aproximadamente 50% en peso seco del recubrimiento de
025 liberación controlada AQ, incluidos todos los valores y subrangos intermedios;
preferiblemente de aproximadamente 2% a aproximadamente 40% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos
intermedios, y mas preferiblemente de aproximadamente 10% a aproximadamente 30%
en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y
30 subrangos intermedios. En ciertas realizaciones, el antiadherente estÆ presenteen la
fonnulación de recubrimiento en una cantidad entre aproximadamente 0% y aproximadamente 20,0% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; en otras realizaciones, en una cantidad de aproximadamente 0% a aproximadamente 12,0% en peso seco del comprimido, incluidos todos los valores y
35 subrangos intermedios; y en otras realizaciones adicionales en una cantidad de
aproximadamente 0,6% a aproximadamente 7,0% en peso seco del comprimido,
incluidos todos los valores y subrangos intermedios.

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Ciertas realizaciones pueden incluir antiespumantes en la composición de recubrimiento de liberación controlada AQ. Ejemplos no limitantes de antiespumantes
ü tiles incluyen aceite de silicio, simeticona y sus mezclas. En al menos una realización,
la simeticona es el antiespumante utilizado en la composición de recubrimiento de liberación controlada AQ. El antiespumante puede estar presente en una cantidad de hasta aproximadamente 0,5% en peso de la composición del recubrimiento de liberación controlada AQ. Por ejemplo, en cierta realizaciOn ci antiespumante estÆ presente en una cantidad entre aproximadamente 0,1% y aproximadamente 0,4% en peso de la coinposición del recubrimiento de liberación controlada AQ, incluidos todos los valores y rangos intermedios. En ciertas realizaciones, ci antiespumante estÆ presente en una cantidad de mÆs de aproximadamente 0% a aproximadamente 3% en peso seco del recubrimiento de iiberaciOn controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones, ci antiespumante estÆpresente en una cantidad de aproximadamente 0,4% a aproximadamente 2% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones, ci antiespumante estÆpresente en una cantidad de aproximadamente 0,8% a aproximadamente 1,5% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios; por ejemplo, incluido 0,9%, aproximadamente 1,0%, aproximadamente 1,1%, aproximadamente 1,2%, aproximadamente 1,3% y aproximadamente 1,4% en peso seco del recubrimiento de liberaciOn controlada AQ. En otras realizaciones, el antiespumante estÆ presente en la formulación de recubrimiento en una cantidad de aproximadamente 0% a aproximadamente 1,2% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; en otras realizaciones en una cantidad de aproximadamente 0% a aproximadamente 0,8% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; y en otras realizaciones adicionales en una cantidad de aproximadamente 0% a aproximadamente 0,2% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; por ejemplo, incluidos aproximadamente 0,01%, aproximadamente 0,02%, aproximadamente 0,03%, aproximadamente 0,04%, aproximadamente 0,05%, aproximadamente 0,06%, aproximadamente 0,07%, aproximadamente 0,08%, aproximadamente 0,09%, aproximadamente 0,10%, aproximadamente 0,11%, aproximadamente 0,12%, aproximadamente 0,13%, aproximadamente 0,14%, aproximadamente 0,15%, aproximadamente 0,16%, aproximadamente 0,17%, aproximadamente 0,18% y aproximadamente 0,19% en peso seco del comprimido.

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Ciertas realizaciones pueden incluir emulsionantes (tambiØn denominados emulsionantes
o emulgentes) en el recubrimiento de Iiberación controlada AQ. Los emulsionantes facilitan la emulsificaciOn durante la fabricación del recubrimiento de liberaeión

5 controlada AQ y tambiØn proporcionan estabilidad de la emulsion durante la vida ütil del
producto. Los ejemplos no limitantes de emulsionantes incluyen materiales de origen natural y sus derivados semisintØticos, como los polisacÆridos, asi como los Østeres de glicerol, los Øteres de celulosa, los Østeres de sorbitÆny los polisorbatos. Las mezclas son factibles. En al menos una realización el emulsionante es Polisorbato 80 (monooleato de
10 polioxietilensorbitÆn) (por ejemplo, TWEENfi 80). El emulsionante puede estar presente
en una cantidad de entre aproximadamente 0% y aproximadamente 0,5% en peso de la composición de recubrimiento de liberaciOn controlada AQ, incluidos todos los valores y subrangos intermedios. Por ejemplo, en ciertas realizaciones, el emulsionante estÆ presente en una cantidad entre aproximadamente 0,1% y aproximadamente 0,3% en peso
15 de la composición del recubrimiento de liberaciOn controlada AQ, incluidos todos los
valores y rangos intermedios. En ciertas realizaciones, el emulsionante estÆpresente en
una cantidad de mÆs de aproximadamente 0% a aproximadamente 2% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones, ci emulsionante estÆpresente en una cantidad de
20 aproximadamente 0,1% a aproximadamente 1% en peso seco del recubrimiento de
!iberación controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones, el emulsionante estÆ presente en una cantidadde aproximadamente 0,25%
a aproximadamente 0,75% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios; por ejemplo, incluido 0,30%,
1025 aproximadamente 0,35%, aproximadamente 0,40%, aproximadamente 0,45%, aproximadamente 0,50%, aproximadamente 0,55%, aproximadamente 0,60%, aproximadamente 0,65% y aproximadamente 0,70% en peso seco del recubrimiento de liberación controlada AQ. En otras realizaciones, ci emulsionante estÆ presente en la formulaciOn de recubrimiento en una cantidad de mÆs de aproximadamente 0% a
30 aproximadamente 0,8% en peso seco del comprimido, incluidos todos los valores y
subrangos intermedios; en otras realizaciones en una cantidad de mÆs de aproximadamente 0% a aproximadamente 0,4% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; y en otras realizaciones adicionales en una cantidad de mÆs de aproximadamente 0% a aproximadamente 0,2% en peso seco del
35 comprimido, incluidos todos los valores y subrangos intermedios; por ejemplo, incluidos
aproximadamente 0,01%, aproximadamente 0,02%, aproximadamente 0,03%, aproximadamente 0,04%, aproximadamente 0,05%, aproximadamente 0,06%,

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aproximadamente 0,07%, aproximadamente 0,08%, aproximadamente 0,09%, aproximadamente 0,10%, aproximadamente 0,11%, aproximadamente 0,12%, aproximadamente 0,13%, aproximadamente 0,14%, aproximadamente 0,15%, aproximadamente 0,16%, aproximadainente 0,17%, aproximadamente 0,18% aproximadamente 0,19% en peso seco del comprimido.

Ciertas realizaciones pueden incluir colorantes en la fOrmula de pelicula de recubrimiento. Dichos colorantes pueden ser colores insolubles en agua (pigmentos). Los pigmentos tienen ciertas ventajas sobre los colorantes solubies en agua en que tienden a ser qulmicamente mÆs estables frente a la luz, proporcionan mejor opacidad y poder de cobertura y optimizan la impermeabilidad de una peilcula dada al vapor de agua. Los ejempios no limitantes de colorantes adecuados incluyen pigmentos de oxido de hierro, dióxido de titanio y lacas de aiuminio. Las mezcias son factibies. En al menos una realización ci pigmento es dióxido de titanio. El pigmento o colorante puede estar presente en una cantidad de entre aproximadamente 0,1% y aproximadamente 10% en peso de la composición de recubrimiento de liberación controlada AQ, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, el pigmento o colorante estÆpresente en una cantidad entre aproximadamente 0,1% y aproximadamente 5%, y en otras realizaciones entre aproximadamente 0,1% y aproximadamente 2% en peso de la composición del recubrimiento de liberación controlada AQ. En ciertas realizaciones, ci colorante estÆ presenteen una cantidad de mÆsde aproximadamente 0% a aproximadamente 20% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones, ci colorante estÆpresente en una cantidad de mas de aproximadamente 0% a aproximadamente 10% en peso seco del recubrimiento de liberaeión controlada AQ, incluidos todos los valores y subrangos intermedios. En otras realizaciones adicionales, ci colorante estÆpresente en una cantidad de aproximadamente 2,2% a aproximadamente 6,2% en peso seco del recubrimiento de liberación controlada AQ, incluidos todos los valores y subrangos intermedios. En ciertas realizaciones, ci colorante estÆ presente en la formulación de recubrimiento en una cantidad de mªs de aproximadamente 0% a aproximadamente 8,0% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; en otras realizaciones en una cantidad de mÆs de aproximadamente 0% a aproximadamente 5,0% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; y en otras realizaciones adicionales en una cantidad de mÆs de aproximadamente 0% a aproximadamente 1,0% en peso seco del comprimido, incluidos todos los valores y subrangos intermedios; por ejemplo, incluidos aproximadamente 0,1%, aproximadamente 0,2%, aproximadamente 0,3%, aproximadamente 0,4%, aproximadamente 0,5%,

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aproximadamente 0,6%, aproximadamente 0,7%, aproximadamente 0,8% y
aproximadamente 0,9% en peso seco del comprimido.

En at menos una realización, el recubrimiento de liberación controlada AQ se hidrata
5 cuando se coloca en agua. En al menos una realización, la forma farmacØutica que se
recubre con el recubrimiento de liberación controlada AQ flota en el agua. En al menos
una realización, la forma farmacØutica de liberación controlada, tras la administraciOn oral a un paciente, proporciona liberación controlada de una cantidad efectiva de bromhidrato de bupropion a al menos una region del tracto gastrointestinal superior del
10 paciente (por ejemplo, el estómago).

En ciertas realizaciones, el recubrimiento de liberación controlada AQ se forma mediante
un proceso que no implica el uso de un disolvente orgÆnico. En dichas realizaciones, la composiciOn del recubrimiento de liberación controlada AQ es con base acuosa y no con
15 disolvente, en contraste con las composiciones de recubrimiento de la tØcnica anterior
que son con base disolvente (por ejemplo, la composición "PharmaPASS").

En ciertas realizaciones, el recubrimiento de liberación controlada AQ del comprimido de bromhidrato de bupropion puede obtenerse de acuerdo con cualquiera de los mØtodos
20 descritos en la presente.

El recubrimiento de liberaciOri controlada AQ se puede aplicar sobre un nücleo que
comprende una cantidad eficaz de la sal bromhidrato de bupropion mediante un proceso,
que implica’la pulverización de la solución o suspensiOn de recubrimiento sobre un lecho
1025 de nücleos de los comprimidos. Algunos ejemplos de equipo adecuado para el
recubrimiento con pelIcula incluyen: ACCELA COTAfi (Manesty Machines, Liverpool,
Reino Unido), HI-COATERfi (Freund Company, Japón), DRIACOATERTM (Driam Metallprodukt GrnbH, Alemania), HTF/150 (GS, Italia) e IDATM (Dumoulin, Francia).
Los ejemplos de unidades que funcionan sobre el principio de lecho fluidizado incluyen:
30 AEROMATICTM (Fielder, Suiza y Reino Unido) y GLATTTM AG (Suiza). En al menos
una reaiización, el aparato usado para el recubrimiento con pelIcula es el ACCELA
COTAfi.

El lIquido de recubrimiento se puede suministrar al aparato de recubrimiento desde una
35 bomba peristÆlticaa la velocidad deseada y pulverizar sobre los nücleos de los
comprimidos rotando o fluyendo. Los nücleos de los comprimidos se precalientan a aproximadamente 30°C. Durante ci proceso de recubrimiento, el intervalo de temperatura

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del producto se mantiene de aproximadamente 25°C a aproximadamente 35°C ajustando
la velocidad de fluj o de entrada y salida del aire, la temperatura de entrada del aire y la velocidad de pulverizaciOn. Se aplica una imica capa de recubrimiento y una vez que se completa la pulverización, los nücleos de los comprimidos recubiertos se secan entre
5 aproximadamente 30°C y aproximadamente 40°C por un periodo de tiempo de entre
aproximadamente 3 y aproximadamente 5 minutos a una velocidad de paila baja y un
flujo de aire bajo. La paila se reajusta para hacer avanzar la velocidad y el secado
continua por un periodo de tiempo de entre aproximadamente 12 y aproximadamente 15

minutos.
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Los nücleos de los comprimidos recubiertos se colocan sobre una bandeja y se curan (tratamiento tØrmico post recubrimiento) en una estufa elØctrica u horno de vapor a una
. temperatura por encima de la temperatura del punto de fusiOn del polietilenglicol o uno
de sus derivados. En ciertas realizaciones, la temperatura de curado es superior al punto
15 de fusion del polietilenglicol o de su derivado. En ciertas realizaciones, el tiempo de
curado es entre aproximadamente 2 y aproximadamente 7 horas. Los comprimidos
recubiertos curados se enfrian posteriormente a temperatura ambiente.

El recubrimiento de liberación controlada AQ es muy versÆtil. La duración y el tiempo
20 del retraso se pueden controlar mediante la velocidad de hidratación y el espesor del
recubrimiento. La velocidad de liberaciOn del fÆrmaco posterior al retrasoSe puede
determinar mediante el espesor y la permeabilidad del recubrimiento hidratado. Por lo
tanto, es posibie regular la velocidad de hidratación y permeabilidad del recubrimiento de Sliberación controlada AQ para que se pueda lograr el perfil deseado de liberaciOn
25 controlada del fÆrmaco. No se prefiere ningtn espesor en particular para ci
recubrimiento, ya que Øste dependera del perfil de liberaciOn controlada deseado. Otros parÆmetros encombinación con ci espesor del recubrimiento incluyen variar las
concentraciones de algunos de los ingredientes de la composiciOn del recubrimiento
estable de la invención descrita y/o variar la temperatura de curado y la duración del
30 curado de los nücleos de los comprimidos recubiertos. El tØcnico con experiencia sabrÆ
quØ parÆmetroso combinaciones de parÆmetroscambiar para lograr un perfil de
liberación controlada deseado.

Como se vera en los ejempios no excluyentes que se describen en ci presente, los
35 recubrimientos usados en ciertas realizaciones de la presente invenciOn son muy
versÆtiles. Por ejemplo, la duración y ci tiempo del periodo de retraso se pueden
controlar mediante la velocidad de hidratación y ci espesor del recubrimiento de

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liberación controlada. Otros parªmetros en combinación con el espesor de los recubrimientos incluyen la variación de las concentraciones de algunos de los ingredientes de las composiciones de recubrimiento de ciertas realizaciones descritas yb
la variación de la temperatura de curado y el periodo de curado de los nücleos de los comprimidos recubiertos. El tØenico con experiencia sabrª quØ parÆmetros o
combinaciones de parÆrnetros cambiar para lograr unperfil de liberación controlada
deseado.

El recubrimiento de barrera contra la humedad
10 En ciertas realizaciones, se aplica una barrera contra la humedad opcional directamente
sobre el recubrimiento de liberación controlada. En otras realizaciones no se incluye una barrera contra la humedad en la forma farmacØutica. En ciertas realizaciones, la barrera contra la humedad comprende un poilmero entØrico (por ejemplo, polimero acrilico), un potenciador de la penetración y opcionalmente un plastificante.

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En ciertas realizaciones, el polimero entØrico es un poilmero acrilico. Por ejemplo, el polimero acrIlico puede ser un copoilmero del Æcidometacrilico tipo C de [poli(Æcido metacrilico, metacrilato de metilo) 1:11 (por ejemplo, EUDRAGITfi L 30 D-55). El copoilmero del Æcido metracrIlicopuede estar presente en una cantidad, que puede variar
20 de aproximadamente 1% a aproximadamente 3% del peso seco del comprimido, incluidos
todos los valores y rangos intermedios, y de aproximadamente 55% a aproximadamente
70% del peso seco de la barrera contra la humedad, incluidos todos los valores y rangos intermedios. Para ci comprimido de liberación extendida de 174 mg de dosis de ciertas realizaciones de la presente invención, ci copoilmero del Æcido metacrilico puede variar
 25 de aproximadamente 2% a aproximadamente 3% del peso seco del comprimido, incluidos
todos los valores y rangos intermedios. Por ejemplo, en el comprimido de 174 mg de
ciertas realizaciones, el copoilmero del Æcido metacrilico estÆ presente en una cantidad de aproximadamente 2,5% del peso seco del comprimido. En lo que se refiere a la barrera
contra la humedad en sí, el copolimero del Æcidometacrilico en el comprimido de 174 mg
30 puede estar presente en una cantidad entre aproximadamente 55% y aproximadamente
70% en peso del peso seco de la barrera contra la humedad, incluidos todos los valores y rangos intermedios. Por ejemplo, en ci comprimido de 174 mg de ciertas realizaciones,
el copolImero del Æcido metacrilico estÆ presenteen una cantidad de aproximadamente
60% del peso seco de la barrera contra Ia humedad. Para el comprimido de liberación
35 extendida de 348 mg de dosis de ciertas realizaciones, la cantidad del copolImero del
Æcido metacrIlicopuede variar de aproximadamente 1,5% a aproximadamente 3% del
peso seco del comprimido, incluidos todos los valores y rangos intermedios. Por ejemplo,

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en el comprimido de 348 mg de ciertas realizaciones, ci copolimero del Æcidometacrilico estÆpresente en una cantidad de aproximadamente 2% del peso seco del comprimido. En
lo que se refiere a la barrera contra la humedad en si, el copoilmero del Æcidometacrilico
en el comprimido de 348 mg estarÆtIpicamente presente en una cantidad entre
5 aproximadamente 55% y aproximadamente 70% del peso seco de la barrera contra la
humedad, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones del comprimido de 348 mg, el copolfmero del Æcidometacrilico estÆ
presente en una cantidad de aproximadamente 60% del peso seco de la barrera contra la humedad. Para el comprimido de liberación extendida de 522 mg de dosis de ciertas
10 realizaciones, la cantidad del copolimero del Æcido metacrilicopuede variar de
aproximadamente 0,5% a aproximadamente 5% del peso seco del comprimido, incluidos
todos los valores y rangos intermedios. Por ejemplo, en el comprimido de 522 mg de
. ciertas realizaciones, la cantidad del copoilmero del Æcidometacrflico estÆpresente en
aproximadamente 2% del peso seco del comprimido. En lo que se refiere a la barrera
15 contra la humedad en si, ci copollinero del Æcido metacrilico en el comprimidode 522 mg
estarÆtIpicamente presente en una cantidad entre aproximadamente 40% y
aproximadamente 80% del peso seco de la barrera contra la humedad. Por ejemplo, en
ciertas realizaciones del comprimido de 522 mg, el copolImero del Æcido metacrilicoestÆ presente en una cantidad de aproximadamente 65% del peso seco de la barrera contra la
20 humedad.

Se sabe en el area que los copoilmeros del Æcidometacrilico se pueden tomar quebradizos
y que los recubrimientos que contienen copoilmeros del Æcidometacrilico se podrIan
hacer mªs elÆsticosy flexibles mediante adición de un plastificante. En ciertas
25 realizaciones la barrera contra la humedad contiene un plastificante. Los ejemplos no
limitantes de plastificantes Ætiiespara ci recubrimiento de barrera contra la humedad de ciertas realizaciones incluyen monoglicØridos acetilados; acetil tributil citrato, butil ftalil
butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil fialil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo;
30 monoglicØrido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de
coiza, aceite de oliva, aceite de sØsamo, citrato de trietilo; alcoholes polibIdricos, glicerol, glicerina, sorbitol, Østeres dc acetato, triacetato de glicerol, acetil trietil citrato, ftalato de dibencilo, ftalato de dihexilo, octil ftalato de butilo, ftalato de di isononilo, oetil ftalato de butilo, azelato de dioctilo, talato epoxidado, trimelitato de triisoctilo, ftalato de
35 dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, ftalato de di-i-deciio, ftalato de
di-n-undecilo, ftalato de di-n-tridecilo, trimelitato de tri-2-etilhexilo, adipato de di-2-etilhexilo, sebacato de di-2-etilhexilo, azelato de di-2-etilhexilo, sebacato de dibutilo,

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oxalato de dietilo, malato de dietilo, fumarato de dietilo, succinato de dibutilo, malonato
de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de glicerol y sus mezclas, polioles (por ejemplo, polietilenglicol) de diversos pesos moleculares y sus mezclas. En ciertas realizaciones, el plastificante en el recubrimiento de barrera contra la humedad
5 comprende una combinación de citrato de trietilo y polietilenglicol 4000 (por ejemplo,
CARBOWAX(V 4000). En algunas de estas realizaciones, la relación entre citrato de
trietilo y polietilenglicol 4000 es aproximadamente 1:2. El plastificante puede estar
presente en el recubrimiento de barrera contra la humedad de ciertas realizaciones en una cantidad que puede variar de aproximadamente 0,2% a aproximadamente 0,5%, incluidos
10 todos los valores y rangos intermedios (por ejemplo, incluido entre aproximadamente
0,3% y aproximadamente 0,4% del peso seco del comprimido). Por ejemplo, en ciertas realizaciones, el plastificante puede estar presente en una cantidad de aproximadamente 0,35% del peso seco del comprimido para un comprimido de 174 mg; en una cantidad de aproximadamente 0,2% a aproximadamente 0,4% del peso seco del comprimido para un
15 comprimido de 348 mg; y en una cantidad de aproximadamente 0,05% a
aproximadamente 0,5% del peso seco del comprimido para un comprimido de 522 mg, incluidos todos los valores y rangos intermedios. En lo que se refiere a la barrera contra
la humedad en si, el plastificante cuando estÆ presente en ciertasrealizaciones puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 30% en peso
20 del peso seco de la barrera contra la humedad, incluidos todos los valores y rangos
intermedios. Por ejemplo, en ciertas realizaciones el plastificante estÆ presente enuna
cantidad entre aproximadamente 10% y aproximadamente 14% del peso seco de la
barrera contra la humedad para comprimidos de liberaciOn extendida de 174 mg, 348 mg
y 522 mg de dosis de la presente invenciOn. Es bien conocido por los tØcnicos en la
 25 materia que dependiendo de la función principal a la que estÆndestinados, los excipientes
que se van a usar en lo.s comprimidos se subclasifican en diferentes grupos. Sin embargo,
un excipiente puede afectar a las propiedades de un fÆrmaco o del comprimidoen su
totalidad de una serie de maneras y por consiguiente muchas sustancias usadas en las formulaciones de comprimidos pueden describirse como multifuncionales. Por ejemplo,
30 el polietilenglicol usado en la combinación plastificante para la barrera contra la humedad
puede sersrir no sOlo para aumentar la hidrofihicidad de la barrera contra la humedad, sino
que tambiØn puede actuar como un deslizante.

En ciertas realizaciones, la barrera contra la humedad puede ademÆscomprender un
35 potenciador de la penetración que puede aumentar su hidrofflicidad y tambiØn puede
actuar como un deslizante. El potenciador de la penetración puede ser una sustancia
hidrófila y se puede seleccionar entre los siguientes ejemplos no limitantes: polimeros

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hidrófilos como hidroxipropilmetilcelulosa, Øteres de celulosa y materiales derivados proteicos de estos poilmeros, los Øteres de celulosa, como hidroxialquilcelulosas, carboxialquilcelulosas y sus mezclas. AdemÆs, se pueden usar poilmeros solubles en
agua sintØticos, como polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de
5 polietileno, polidextrosa soluble en agua, sacridos y polisacridos, como puilulan,
dextrano, sacarosa, giucosa, lactosa, fructosa, manitol, manosa, galactosa, sorbitol y sus mezclas. En al menos una realización de la presente invención, ci polimero hidrófiio comprende hidroxipropilmetilcelulosa. Otros ejemplos no limitantes de potenciadores de
la penetración que se pueden usar en la barrera contra la humedad de ciertas realizaciones
10 incluyen sales de metales alcalinos como óxido de aluminio, carbonato de litio, cloruro
de sodio, bromuro de sodio, cioruro de potasio, sulfato de potasio, fosfato de potasio,
acetato de sodio, citrato de sodio y sus mezclas. Los potenciadores de la penetración o formadores de poros pueden ser poilmeros que son solubles en ci ambiente de uso, como
los CARBOWAXfi, CARBOPOLfi y sus mezclas. Ejempios no limitantes de
15 formadores de poros incluyen dioles, polioles, alcoholes polihIdricos,
poliaiquilenglicoies, poliglicoles, poli(a-w)alquilendioles y sus mezclas. Otros potenciadores de la penetración que pueden ser ütiles en las formulaciones de la presente invención incluyen almidón, almidOn modificado y derivados del almidón, gomas,
incluidas, pero no exciusivamente, goma xantano, Æcido alginico,otros alginatos,
20 bentonita, veegum (silicato de aluminio y magnesio), agar, goma guar, goma de
aigarrobo, goma arÆbiga, quincepsyllium, semilla de lino, goma de quimbombo, arabinogalactano, pectina, goma tragacanto, escleroglucano, dextrano, amilosa,
amilopectina, dextrina, polivinilpirrolidona reticulada, resinas de intercambio ionico,
como polimetacrilato de potasio, carragenina, carragenina kappa, carragenina lambda,
5 goma karaya, goma biosintØtica, y sus mezclas. Otros potenciadores de la penetración
incluyen materiales ütiles para hacer lÆminasmicroporosas en los ambientes de uso,
como policarbonatos compuestos de poliØsteres lineales del Æcidocarbónico en los que
los grupos carbonato reaparecen en la cadena polimØrica, materiales microporosos como bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas, copoilmeros
30 modacrulicos microporosos, estireno-acrIlico microporoso y sus copoilmeros,
polisuifonas porosas, poli(vinilideno) halogenado, policloroØteres, poilmeros de acetal, poliØsteres preparados por esterificación de un Æcidodicarboxilico o anhIdrido con un alquilenpoliol, poli(sulfuros de aiquileno), fenólicos, poliØsteres, polImeros porosos asimØtricos, polimeros olefmnicos reticulados, homopolImeros hidrOfiios microporosos,
35 copolfmeros o interpolfmeros con una menor densidad aparente y otros materiales
similares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas), poli(benzimidazoles), colodión, proteinas regeneradas, poli(vini!pirrolidona) reticulada

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semisólida, dióxido de siliclo, silice coloidal, celulosa microcristalina y sus mezclas. En
al menos una realización de la invención el potenciador de la penetración es dióxido de silicio (por ejemplo, SYLOIDfi 244FP). La cantidad de potenciador de la penetración
puede variar de aproximadamente 0,5% a aproximadamente 1% en peso del peso seco del
5 comprimido, incluidos todos los valores y rangos intermedios, y de aproximadamente
25% a aproximadamente 30% en peso del peso seco de la barrera contra la humedad, incluidos todos los valores y rangos intermedios. Para los comprimidos de liberación extendida de 174 mg de dosis o los comprimidos de liberación extendida de 348 mg de
dosis de ciertas realizaciones de la invención, el potenciador de la penetración puede estar
10 presente en una cantidad de aproximadamente 0,5% a aproximadamente 2% del peso
seco del comprimido, incluidos todos los valores y rangos intermedios, y de aproximadamente 20% a aproximadamente 40% en peso del peso seco de la barrera
contra la humedad, incluidos todos los valores y rangos intermedios. Por ejemplo, en
ciertas realizaciones del comprimido de 174 mg de dosis, ci potenciador de la penetraciOn
15 estÆ presenteen una cantidad entre aproximadamente 25% y aproximadamente 30% en
peso del peso seco de la barrera contra la humedad. Para los comprimidos de Iiberación extendida de 348 mg de dosis de la invención, el potenciador de la penetraciOn puede
estar presente en una cantidad que puede variar de aproximadamente 0,5% a aproximadamente 2% en peso del peso seco del comprimido y de aproximadamente 20%
20 a aproximadamente 40% en peso del peso seco de la barrera contra la humedad. Por
ejemplo, en ciertas realizaciones del comprimido de 348 mg de dosis, el potenciador de la penetración estÆ presente en una cantidad entre aproximadamente 25% y
aproximadamente 30% en peso del peso seco de la barrera contra la humedad. Para los comprimidos de liberación extendida de 522 mg de dosis de la invención, ci potenciador
 25 de la penetración puede estar presente en una cantidad que puede variar de
aproximadamente 0,1% a aproximadamente 2% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios, y de aproximadamente 20% a aproximadamente 40% en peso del peso seco de la barrera contra la humedad, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones del
30 comprimido de 522 mg de dosis, el potenciador de la penetración estÆpresente en una
cantidad entre aproximadamente 25% y aproximadamente 30% en peso del peso seco de
la barrera contra la humedad.

En al menos una realización de la invención, la reiación copolfmero del Æcido
35 metacrIlico:plastificante:potenciador de la penetración en la barrera contra la humedad es
aproximadamente 13:2:5.

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En ciertas realizaciones, la barrera contra la humedad de la forma fannacØutica de bromhidrato de bupropion puede obtenerse de acuerdo con cualquiera de los mØtodos descritos en la presente.

5 La preparaciOn y aplicación del proceso de la barrera contra la humedad pueden ser las
siguientes. El plastificante opcional (por ejemplo, una combinación de polietilenglicol
4000 y citrato de trietilo), Se puede agregar primero al agua y mezclar la mezcla hasta homogeneizar. DespuØs el copoilmero del Æcido metacrulico (porejemplo, EUDRAGITfi
L 30 D-55), se tamiza y se agrega a la mezcla plastificante y se mezcla hasta
10 homogeneizar. En un recipiente separado se disuelve el potenciador de La penetraciOn
(por ejemplo, dióxido de silicio) en agua hasta que se logra una mezcla homogØnea.
DespuØs se combinan el plastificante y La mezcla de copolImero del ÆcidometacrIlico con
. la solución del potenciador de la penetración y se mezcla hasta homogeneizar. La
solución de barrera contra la humedad resultante se pulveriza luego sobre los nücleos de
15 los comprimidos recubiertos con el recubrimiento de liberaciOn controlada usando un
aparato de lecho fluidizado revestidor de comprimidos u otro aparato de recubrimiento
adecuado conocido en el area hasta que se logra el aumento de peso deseado. Los
comprimidos recubiertos con la barrera contra la humedad se secan posteriormente antes
de envasar.
20

La barrera contra la humedad se aplica a los nücleos de los comprimidos con
recubrimiento de liberación controlada de tal manera que el aumento de peso sea no mªs
de aproximadamente 6% del peso seco del comprimido para los comprimidos de
Iiberación extendida de 174 mg, 348 mg y 522 mg de ciertas realizaciones de la presente
- 25 invención. En ciertas realizaciones, el aumento de peso no es mÆsde aproximadamente
3,5% del peso seco del comprimido para los comprimidos de liberacIón extendida de 174
mg, 348 mg y 522 mg. La cantidad de barrera contra la humedad aplicada en general no
torna al comprimido de liberación extendida descrito aqul significativamente mÆs
resistente al liquido gÆstrico. Sinembargo, en ciertas realizaciones, la barrera contra la
30 humedad puede tener repercusión sobre las caracterIsticas de liberación del fªrmaco.

La barrera contra la humedad, como se usa en ciertas realizaciones, no actüa
habitualmente como un recubrimiento entØrico. Aunque en el area se hace referencia y se usa el copolimero del Æcidometacrflico, EUDRAGITfi L 30 D-55, en formulaciones de
35 recubrimiento entØrico, su funcionalidad depende de la formulación y de la cantidad de
material aplicado. Como se sabe en el area, un recubrimiento entØrico se aplica cuando
un fÆrmaco puedeser destruido o inactivado pot losjugos gªstricos o cuando el fÆrmaco

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puede irritar la mucosa gÆstriea. Para cumplir con losrequisitos de un recubrimiento entØrico, la prueba segün se describe en la USP (mØtodo A o B) estipula que despuØs de 2 horas en medio Æcido (HC10,1 N), ningün valor individual de al menos seis experimentos excede de aproximadamente 10% del fÆrmacoactivo disuelto y no menos de
5 aproximadamente 75% se disuelve a los aproximadamente 45 minutos a pH 6,8
aproximadamente. La barrera contra la humedad de ciertas realizaciones no cumple con
este requisito por las razones siguientes aunque la sal bromhidrato de bupropion no es afectada negativamente en los medios Æeidos ni esirritante para la mucosa gÆstrica: (1)
para obtener integridad entØrica con una pelfcula que contiene EUDRAGITfi L 30 D-55,
10 se recomienda un aumento de peso de aproximadamente 6% a aproximadamente 8%
basado en el polImero seco por unidad de dosificación. La cantidad de sólidos de EUDRAGITfi L 30 D-55 aplicada sobre los nücleos de los comprimidos con
recubrimiento de liberaciOn controlada no es mÆs de aproximadamente 6%y en al menos una realizaciOn, no es mÆs deaproximadamente 3%, (2) si fuera necesaria la integridad
15 entØrica, la prueba de disolución para el producto terminado (es decir, los nücleos de los
comprimidos recubiertos con barrera contra la humedad) on el tiempo de muestreo a las 2 horas no estipularla un limite de no mÆs deaproximadamente 20%, y (3) las pruebas analIticas realizadas sobre estos recubrimientos indican que los recubrimientos no
cumplen con todos los requisitos de la prueba como un producto con recubrimiento
20 entØrico segün se define por los mØtodos de prueba de la USP.

El cornprimido XL de ciertas realizaciones de la invención proporciona una liberación
extendida de la sal bromhidrato de bupropion. En al menos una realización, no hay
presente ningün agente formador de poros en la formulación de recubrimiento XL. En
1025 ciertas realizaciones se proporciona una formulación de bromhidrato de bupropion de
liberación extendida taT que despuØs de aproximadamente 2 horas, se libera no mÆsde aproximadamente 20% del contenido de bromhidrato de bupropion. Por ejemplo, en
ciertas realizaciones, se libera de aproximadamente 2% a aproximadamente 18%, preferentemente de aproximadamente 4% a aproximadamente 8% o aproximadamente
30 5% del contenido de bromhidrato de bupropion despuØs de aproximadamente 2 horas.
DespuØs de aproximadamente 4 horas, se libera de aproximadamente 15% a aproximadamente 45% del contenido de bromhidrato de bupropion. Por ejemplo, en
ciertas realizaciones, se libera de aproximadamente 21% a aproximadamente 37%, ma’s preferentemente de aproximadamente 28% a aproximadamente 34% o aproximadamente
35 32% del contenido de broinhidrato de bupropion despuØs de aproximadamente 4 horas.
Despuds de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90% del contenido de bromhidrato de bupropion. Por ejemplo, en

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ciertas realizaciones, se libera de aproximadamente 60% a aproximadamente 85%, de aproximadamente 68% a aproximadamente 74% o aproximadamente 74% del contenido
de bromhidrato de bupropion despuØs de aproximadamente 8 horas. DespuØs de aproximadamente 16 horas se libera no menos de aproximadamente 80% del contenido
5 de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera el contenido
de bromhidrato de bupropion despuØs de aproximadamente 16 horas.

AdemÆs, en ciertas realizacionesSe proporcionan comprimidos de liberación extendida
en los que despuºs de aproximadamente 2 horas se libera no mÆsde aproximadamente
10 40% (por ejemplo, aproximadamente 33%) del brornhidrato de bupropion; despuØs de
aproximadamente 4 horas se libera de aproximadamente 40% a aproximadamente 75%
del bromhidrato de bupropion (por ejemplo, aproximadamente 59%); despuØs de Saproximadamente 8 horas se libera al menos aproximadamente 75% del bromhidrato de bupropion (por ejemplo, aproximadamente 91%); y despuØs de aproximadamente 16
15 horas se libera al menos aproximadamente 85% del bromhidrato de bupropion (por
ejemplo, aproximadamente 97%). En todos los casos cuando aqui se proporcionan
perfiles de disolución reales o profØticos esto significa que el medicamento posee dicho
perfil en al menos un medio de disolución en las condiciones prescritas como las
identificadas aqul y que son bien conocidas por los tØcnicos con experiencia on ci tema.
20 Dichos medios de disolución, condiciones de disoluciOn y aparato para realizarla se
especifican en la farmacopea de los Estados Unidos (USP) y sus contrapartes europea y japonesa. AdemÆs,se proporcionan ejemplos especificos en esta solicitud.

Comprimidos de absorciOn mejorada (EA)
25 En ciertas realizaciones de la presente invenciÆn, seproporciona un comprimido de
absorción mejorada (EA) que tiene un nücleo que comprende una sal bromhidrato de bupropion y excipientes convencionales, en donde la sal bromhidrato de bupropion proporciona una reducción de las incidencias y/o de la gravedad de las crisis convulsivas inducidas por bupropion, y es mÆsestable, en eomparación con cantidades molares
30 equivalentes de ciorhidrato de bupropion. El nücieo estÆ rodeado por un recubrimiento
EA, que controla la liberación de la sal bromhidrato de bupropion. En ciertas
realizaciones, ci recubrimiento EA consta de una capa. Una ventaja del comprimido EA incluye la menor cantidad de fÆrmacorequerida on la composición para que sea eficaz,
que a su vez puede dar lugar a una reducción de los efectos colaterales. El comprimido
35 EA puede comprender opcionalmente uno o mÆs recubrimientosfuncionales o no
funcionales adicionales alrededor del nücleo o el recubrimiento EA.

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El nücleo EA

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El nücleo del comprimido EA comprende una cantidad eficaz de una sal bromhidrato de bupropion, un aglutinante y un lubricante y puede contener otros excipientes inertes convencionales. En ciertas realizaciones, el nücleo del comprimido EA puede
5 comprender los mismos excipientes y Se puede procesar de la misma manera que el
nücleo del comprimido de liberaciOn extendida. La cantidad de sal bromhidrato de
bupropion presente en el nücleo BA puede variar entre aproximadamente 40% y aproximadamente 99% en peso del peso seco del comprimido BA, incluidos todos los valores y rangos interinedios. El comprimido EA comprende una cantidad eficaz de la
10 sal bromhidrato de bupropion que puede variar de aproximadamente 50 mg a
aproximadamente 1000 mg, ineluidos 100, 150, 200, 250, 300, 350, 400, 450, 500, 510,
520, 530, 540, 550, 560, 570, 580, 590, 600, 650, 700, 750, 800, 85, 900, 950 mg y todos
los valores y rarigos intermedios. Por ejemplo, ciertas realizaciones del comprimido EA pueden comprender aproximadamente 150 mg, aproximadamente 300 mg o
15 aproximadamente 450 mg de bromhidrato de bupropion. Para un comprimido de 150 mg
de dosis el bromhidrato de bupropion puede estar presente en una cantidad entre aproximadamente 76% y aproximadamente 84% en peso del peso seco del comprimido.
Para una dosis de 300 mg, el bromhidrato de bupropion puede estar presente en una
cantidad entre aproximadamente 80% y aproximadamente 83% en peso del peso seco del
20 comprimido. Para una dosis de 450 mg, el bromhidrato de bupropion puede estar
presente en una cantidad entre aproximadamente 75% y aproximadamente 90% en peso
del peso seco del comprimido. Para los comprimidos EA de bromhidrato de bupropion
de 150 mg, 300 mg y 450 mg de dosis de ciertas realizaciones de la invención, el bromhidrato de bupropion puede estar presente en una cantidad de aproximadamente’

4025 94% en peso del nücleo seco para cada dosis.

El recubrimiento del comprimido BA
Los nücleos de los comprimidos EA se pueden recubrir en una etapa. El recubrimiento
EA se aplica directamente sobre la superficie de los nücleos de los comprimidos y actüa
30 controlando la liberación de la sal bromhidrato de bupropion. El recubrimiento EA es
una capa semipermeable que comprende un polImero formador de pelicula insoluble en
agua y permeable al agua, un polimero soluble en agua y opcionalmente un plastificante.
En ciertas realizaciones, el recubrimiento EA puede comprender los mismos ingredientes
y se puede procesar de la misma manera que el recubrimiento XL de liberación
35 controlada.

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Los ej emplos no limitantes de polimeros formadores de pelicula, insolubles en agua y permeables al agua fitiles para el recubrimiento EA incluyen aquellos que se pueden usar en el recubrimiento XL de liberaeión controlada. La cantidad de polimero formador de pelicula insoluble en agua y permeable at agua puede variar de aproximadamente 1% a
5 aproximadamente 8% en peso del peso seco del comprimido, incluidos todos los valores
y rangos intermedios. Por ejemplo, en ciertas realizaciones la cantidad de polimero
formador de pelicula, insoluble en agua y permeable at agua es de aproximadamente 2%
a aproximadamente 6% en peso del peso seco del comprimido. Para ciertas realizaciones
de los comprimidos EA de 150 mg, 300 mg o 450 mg de dosis de ciertas realizaciones de
10 la invención, la cantidad de polimero formador de pelicula, insoluble en agua y
permeable at agua es de aproximadamente 1% a aproximadamente 15% en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones de los comprimidos EA de
150 mg de dosis, la cantidad de polimero formador de pelicula, insoluble en agua y permeable at agua estÆ presente en aproximadamente 10,5% en peso del peso seco del
15 comprimido. En to que se refiere at recubrimiento EA en si, la cantidad de polimero
formador de pelicula, insoluble en agua y permeable at agua en ciertas realizaciones de
los comprimidos EA de 150 mg de dosis es de aproximadamente 35% a
aproximadamente 60% en peso del peso seco del recubrimiento EA. Por ejemplo, en
ciertas realizaciones del comprimido EA de 150 mg de dosis, la cantidad de polimero
20 insoluble en agua y permeable at agua presente es de aproximadamente 55% en peso del
peso seco del recubrimiento EA. Para ciertas realizaciones del comprimido EA de 300
mg de dosis de la invención, la cantidad de polimero formador de pelicula, insoluble en
agua y permeable at agua es de aproximadamente 1% a aproximadamente 8% en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones del comprimido de EA
25 de 300 mg de dosis, la cantidad de poilmero formador de pelicula, insoluble en agua y
permeable at agua presente es de aproximadamente 6,3% en peso del peso seco del comprimido. En to que se refiere at recubrimiento EA en si, el polimero formador de pelicula, insoluble en agua y permeable at agua en el comprimido EA de 300 mg de dosis puede estar presente en una cantidad de aproximadamente 55% en peso del peso seco del
30 recubrimiento BA. En ciertas realizaciones de los comprimidos EA de 450 mg de dosis
de la invención, la cantidad de polimero formador de pelicula, insoluble en agua y permeable at agua es de aproximadamente 0,5% a aproximadamente 10% en peso del
peso seco del comprimido y en otras realizaciones de aproximadamente 1% a aproximadamente 6% en peso del peso seco del comprimido. En to que se refiere at
35 recubrimiento BA en si, el polimero formador de pelicula, insoluble en agua y permeable
at agua en el comprimido EA de 450 mg de dosis puede estar presente en una cantidad de aproximadamente 37% en peso del peso seco del recubrimiento EA.

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En ciertas realizaciones, el recubrimiento EA contiene ademÆs un plastificante. Los ejemplos no limitantes de plastificantes que se pueden usar en el recubrimiento EA
incluyen aquellos que se pueden usar en el recubrimiento XL de liberaciOn controlada. La
5 cantidad de plastificante que se puede usar en el recubrimiento EA puede variar en una
cantidad entre aproximadamente 0,5% y aproximadamente 4% en peso del peso seco del comprimido, incluidos todos los valores y rangos intermedios. En otra realización de la invención, cuando se usa una mezela de dos plastificantes, la relación de los dos plastificantes puede variar de aproximadamente 5:95 a aproximadamente 95:5, incluidos
10 todos los valores y rangos intermedios. En al menos una realización de la invención, el
plastificante es polietilenglicol 4000, sebacato de dibutilo o sus rnezclas. La relación polietilenglicol 4000:sebacato de dibutilo puede variar de aproximadamente 5:95 a aproximadamente 95:5. Para ciertas realizaciones del comprimido EA de 150 mg de dosis
de la invención, la cantidad de plastificante presente en el recubrimiento EA es de
15 aproximadamente 0,5% a aproximadamente 4% en peso del peso seco del comprimido.
Por ejemplo, en ciertas realizaciones del comprimido EA de 150 mg de dosis, la cantidad
de plastificante presente es de aproximadamente 3,1% en peso del peso seco del
comprimido. Para ciertas realizaciones del comprimido EA de 300 mg de dosis de la invencion, la cantidad de plastificante presente es de aproximadamente 0,5% a 3% en
20 peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones del
comprimido EA de 300 mg de dosis, la cantidad de plastificante presente es de aproximadamente 2,0% en peso del peso seco del comprimido. Para ciertas realizaciones
del comprimido BA de 450 mg de dosis de la invención, la cantidad de plastificante
presente es de aproximadamente 0,5% a 4% en peso del peso seco del comprimido. Para ciertas realizaciones de las formas farmacØuticas de 150 mg, 300 mg y 450 mg, el plastificante estÆpresente en una cantidad entre aproximadamente 6% y
aproximadamente 30% en peso del peso seco del recubrimiento BA. Per ejemplo, en
ciertas realizaciones la cantidad de plastificante presente es de aproximadamente 17% en peso del peso seco del recubrimiento BA.
30

Los ejemplos no limitantes de polImeros solubies en agua ütiles para el recubrimiento EA incluyen aquellos que se pueden usar en el recubrimiento XL de liberación controlada. En
al menos una realización de la invención, ci polImero soluble en agua es
polivinilpirrolidona (por ejemplo, Povidonafi USP) cuya cantidad puede variar de
35 aproximadamente 1,5% a aproximadamente 10% en peso del peso seco del comprimido,
incluidos todos los valores y rangos intermedios. En lo que se refiere al recubrimiento
EA en sf, la cantidad de poilmero soluble en agua presente puede variar de

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aproximadamente 20% a aproximadamente 50% en peso del peso seco del recubrimiento EA. Para ciertas realizaciones del comprimido EA de 150 mg de dosis de la invención, la cantidad de polimero soluble en agua presente es de aproximadamente 1,5% a aproximadamente 10% en peso del peso seco del comprimido o de aproximadamente
5 20% a aproximadamente 50% en peso del peso seco del recubrimiento EA. Por ejemplo,
en ciertas realizaciones del comprimido EA de 150 mg de dosis, el polimero soluble en
agua estÆpresente en una cantidad de aproximadamente 28% en peso del peso seco del recubrimiento EA. Para ciertas realizaciones del comprimido EA de 300 mg de dosis de
la invención, la cantidad de polimero soluble en agua presente es de aproximadamente
10 1,5% a aproximadamente 10% del peso seco del comprimido o de aproximadamente 20%
a aproximadamente 50% del peso seco del recubrimiento BA. Por ejemplo, en ciertas realizaciones del comprimido EA de 300 mg de dosis, el polimero soluble en agua estÆ
presente en una cantidad de aproximadamente 28% en peso del peso seco del Srecubrimiento EA. Para ciertas realizaciones del comprimido BA de 450 mg de dosis de
15 la invenciOn, la cantidad de polimero soluble en agua presente es de aproximadamente
2% a aproximadamente 5% del peso seco del comprimido o de aproximadamente 40% a aproximadamente 50% del peso seco del recubrimiento EA.

La relaciOn polimero formador de pelicula, insoluble en agua y permeable al
20 agua:plastificante:pollmero soluble en agua para el recubrimiento del comprimido EA
tlpicamente variara de aproximadamente 3:1:4 a aproximadamente 5:1:2, incluidos todos
los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, la relación
polimero formador de pelicula, insoluble en agua y permeable al
agua:plastificante:polimero soluble en agua para el recubrimiento del comprimido EA es
25 de aproximadamente 4:1:3. En al menos una realización del recubrimiento del
comprimido BA, la relación polimero formador de pelicula, insoluble en agua y
permeable al agua:plastificante:polfmero soluble en agua es de aproximadamente 7:2:6 a aproximadamente 19:5:18, y en otra realizaciOn es de aproximadamente 13:4:12. En al
menos una realización de la forma farmacØutica de 450 mg, la relaciOn polimero
30 formador de pelicula, insoluble en agua y permeable al agua:plastificante:polImero
soluble en agua para el recubrimiento EA es de aproximadamente 13:6:16.

En ciertas realizaciones, el recubrimiento EA de la forma farmacØutica de bromhidrato de bupropion puede obtenerse de acuerdo con cualquiera de los mtodos descritos en la
35 presente para ci recubrimiento XL de liberaciOn controlada.

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Dependiendo de la disolueión o del perfil de liberación in vivo deseados, el aumento del peso despuØs de recubrir el nücieo del comprimido con ci recubrimiento EA puede variar
de aproximadamente 3% a aproximadamente 30% del peso del nücleo del comprimido
seco, incluidos todos los valores y rangos intermedios. Para ciertas realizaciones del
5 comprimido EA de 150 mg de dosis de la invención el aumento de peso es de
aproximadamente 8% a aproximadamente 20% del peso del nücleo del comprimido seco. Por ejemplo, en ciertas rŁalizaciones delcomprimido EA de 150 mg de dosis, ci aumento
de peso es aproximadamente 14% del peso del niicleo del comprimido seco. Para ciertas realizaciones del comprimido BA de 300 mg de dosis de la invención ci aumento de peso
10 es de aproximadamente 10% a aproximadamente 15% del peso del nücleo del
comprimido seco. Por ejemplo, en ciertas realizaciones del comprimido BA de 300 mg
de dosis, ci aumento de peso es aproximadamente 13% del peso del nücleo del
comprimido seco. Para ciertas realizaciones del comprimido BA de 450 mg de dosis de
la invenciOn el aumento de peso es de aproximadamente 5% a aproximadamente 15% del
15 peso del nÆcleodel comprimido seco. Por ejemplo, en ciertas realizaciones del
comprimido BA de 450 mg de dosis, ci aumento de peso es aproximadamente 8,5% del
peso del niicleo del comprimido seco.

El comprimido EA proporciona una absorción mejorada de la sal bromhidrato de
20 bupropion donde no hay habitualmente agente formador de poros presente en la
formulación. Se proporciona una formulación de bromhidrato de bupropion de absorción mejorada tal que despuØs de aproximadamente 2 horas, se libera no mÆs de aproximadamente 25% del contenido de bromhidrato de bupropion. Por ejemplo, en
ciertas realizaciones se libera de aproximadamente 10% a aproximadamente 20% del
1025 contenido de bromhidrato de bupropion despues de aproximadamente 2 horas. DespuØs
de aproximadamente 4 horas, se libera de aproximadamente 25% a aproximadamente
55% del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se
libera de aproximadamente 30% a aproximadamente 50% del contenido de bromhidrato
de bupropion despues de aproximadamente 4 horas. Despuºs de aproximadamente 8
30 horas, se libera mÆsde aproximadamente 60% del contenido de bromhidrato de
bupropion. Por ejemplo, en ciertas realizaciones se libera de aproximadamente 70% a aproximadamente 90% del contenido de bromhidrato de bupropion despuØs de aproximadamente 8 horas. DespuØs de aproximadamente 16 horas, se libera mÆs de aproximadamente 70% del contenido de bromhidrato de bupropion. Por ejemplo, en
35 ciertas realizaciones se libera mÆsde aproximadamente 80% del contenido de
bromhidrato de bupropion despuØs de aproximadamente 16 horas.

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En ciertas realizaciones, se proporciona una formulación de absorción mejorada en la que se libera no mÆs deaproximadamente 40% despuØs de aproximadamente 2 horas; despuØs de aproximadamente 4 horns, se libera de aproximadamente 40% a aproximadamente 75%; despuØs de aproximadamente 8 horas, se libera aproximadamente 75%; y despuØs de aproximadamente 16 horas, se libera al menos aproximadamente 85%. Por ejemplo, en al menos una realización, el perfil de liberación de bromhidrato de
bupropion es de aproximadamente 33% despuØs de aproximadamente 2 horas; aproximadamente 59% despues de aproximadamente 4 horas; aproximadamente 91%
despuØs de. aproximadamente 8 horas; y aproximadamente 97% despuØs de
10 aproximadamente 16 horas.

Matriz de liberación controlada
En otras realizaciones de la presente invención, se proporciona una matriz de liberación controlada cuya cinØtica de liberaciOn del fÆrmacodesde el nücleo de la matriz es
15 dependiente al menos en parte de las propiedades de difusión y/o de erosion de los
excipientes dentro de la composición. En esta realizaciOn, las matrices de liberación controlada contienen una cantidad eficaz de una sal bromhidrato de bupropion y al menos
un excipiente farmacØuticamente aceptable. La cantidad de sal bromhidrato de bupropion presente en la matriz de liberación controlada puede variar en una cantidad entre
20 aproximadamente 40% y aproximadamente 90% en peso del peso seco del comprimido,
incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci bromhidrato de bupropion estª presente en una cantidad de aproximadamente 60% a aproximadamente 80%, y en otra realización en aproximadamente 70% en peso del peso
seco del comprimido de matriz. La matriz de liberación controlada puede ser
1025 multiparticulada o uniparticulada y se puede recubrir con al menos un recubrimiento
funcional o no funcional, o un recubrimiento de liberación inmediata que contiene otro
fÆrmaco. Los recubrimientos funcionales incluyen a modo de ejemplo recubrimientos polimØricos de liberación controlada, recubrimientos polimØricos entØricos y similares.
Los recubrimientos no funcionales son recubrimientos que no afectan a la liberaciOn del
30 farmaco pero que afectan a otras propiedades (por ejemplo, pueden mejorar la quImica, la
biologIa o el aspecto fIsico de la formulación de liberación controlada). Los tØcnicos con experiencia en ci area farmacØutica y ci diseflo de medicamentos estÆn al tantode las
matrices de liberaciOn controlada que se utilizan convencionalmente en las
composiciones farmacØutieas orales adoptadas para la liberaciOn controlada y de los
35 medios para su preparaciOn.

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Los excipientes adecuados para usar en dichas matrices de liberación controlada son conocidos por los tØcnicos con experiencia en el tema e incluyen, a modo de ejemplo, materiales resistentes a la liberación o de liberaciOn controlada como polimeros
hidrófobos, polimeros hidrófilos, materiales lipófflos y sus mezclas. Los ejemplos no
5 limitantes de componentes hidrófobos o lipófilos incluyen monoestearato de glicerilo,
mezclas de monoestearato de glicerilo y monopalmitato de glicerilo (MYVAPLEXTM, Eastman Fine Chemical Company), monooleato de glicerilo, una mezela de mono, di y triglicØridos (ATMULTM 84S), monolaurato de glicerilo, parafina, cera blanca, Æcidos carboxilicos de cadena larga, Østeres de Æcidos carboxilicos de cadenalarga, alcoholes de
10 Æcidoscarboxilicos de cadena larga y sus mezelas. Los Æcidos carboxilicosde cadena
larga pueden contener de aproximadamente 6 a aproximadamente 30 Ætomos de carbono;
en ciertas realizaciones al menos aproximadamente 12 Ætomosde carbono, y en otras realizaciones de aproximadamente 12 a aproximadamente 22 Ætomosde carbono. En algunas realizaciones esta cadena carbonada estÆ totalmentesaturada y no es ramificada,
15 mientras otras contienen uno o mÆsenlaces dobles. En al menos una realización los
Æcidos carboxflieosde cadena larga contienen anillos de aproximadamente 3 carbonos o grupos hidroxilo. Los ejemplos no limitantes de ªcidos saturados de cadena lineal
incluyen Æcido n-dodecanoico,Æcido n-tetradecanoico,Æcido n-hexadecanoico, Æcido caproico, Æcido caprIlico,ÆcidocÆprico,ÆcidolÆurico,ªcido mirIstico, ÆcidopalmItico,
20 Æcidoestearico, Æcidoaraquldico, Æcido behØnico, ªcido montÆnico, Æcido meilsicoy sus
mezclas. TambiØn son ütiles los Æcidos monocarboxIlicosinsaturados monoolefinicos de
cadena lineal. Los ejemplos no limitantes de Østos incluyen Æcido oleico,Æcido
gadoleico, Æcido erUcicoy mezclas de los mismos. TambiØn son ütiles los Æcidos monocarboxIlicos insaturados (poliolefInicos) de cadena lineal. Los ejemplos no
1025 limitantes de Østos incluyen Æcidolinoleico, ÆcidolinolØnico, ªcido araquidónico, Æcido
behenólico y sus mezclas. Los Æcidosramificados Ætilesincluyen, por ej emplo, Æcido diacetiltartÆrico. Los ejemplos no limitantes de Østeres de Æcidoscarboxilicos de cadena
larga incluyen monoestearatos de glicerilo; monopalmitatos de glicerilo; mezclas de monoestearato de glicerilo y monopalmitato de glicerilo (MYVAPLEXTM 600, Eastman
30 Fine Chemical Company); monolinoleato de glicerilo; monooleato de glicerilo; mezclas
de monopalmitato de glicerilo, monoestereato de glicerilo, monooleato de glicerilo y monolinoleato de glicerilo (MYVEROLTM 18-92, Eastman Fine Chemical Company); monolinolenato de glicerilo; monogadoleato de glicerilo; mezclas de monopalmitato de glicerilo, monoestearato de glicerilo, monooleato de glicerilo, monolinoleato de glicerilo,
35 monolinolenato de glicerilo y monogadoleato de glicerilo (MYVEROLTM 18-99,
Eastman Fine Chemical Company); glicØridos acetilados como monoglicØridos acetilados destilados (MYVACETTI’ 5-07, 7-07 y 9-45, Eastman Fine Chemical Company);

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mezclas de monoØsteres de propilenglicol, monoglicØridos destilados, estearoil lactilato
de sodio y dióxido de silicio (MYVATEXTM TL, Eastman Fine Chemical Company); mezclas de monoØsteres de propilenglicol, monogliceridos clestilados, estearoil lactilato
de sodio y dióxido de silicio (MYVATEXTM TL, Eastman Fine Chemical Company) d-
5 alfa tocoferil polietilenglicol 1000 succinato (Vitamina E TPGS, Eastman Chemical
Company); mezclas de Østeres de mono y digliceridos como ATMULTM (Humko
Chemical Division de Witco Chemical); estearoil lactilato de calcio; mono y diglicØridos etoxilados; mono y diglicØridos lactados; ester lactilato de ÆcidocarboxIlico de glicerol y propilenglicol; Østeres lactulicos de ÆcidoscarboxIlicos de cadena larga; Østeres de
10 poliglicerol de ÆcidoscarboxIlicos de cadena larga, mono y diØsteres de propilenglicol de
Æcidoscarboxulicos de cadena larga; estearoil lactilato de sodio; monoestearato de
sorbitÆn; monooleatode sorbitÆn; otros ºsteres de sorbitÆnde Æcidoscarboxilicos de
cadena larga; monoglicØridos succinilados; citrato de estearil monoglicerilo; heptanoato Sdeestearilo; Østeres cetIlicos de ceras; octanoato de cetearilo; Østeres C10-C30 de
15 colesterol/lavosterol; Østeres de sacarosa de Æcidoscarboxflicos de cadena larga; y sus
mezclas. Los alcoholes ütiles como excipientes para las matrices de liberación controlada pueden incluir las formas hidroxilo de los Æcidos carboxIlicosejemplificados antes y
tambiØn el alcohol cetear{lico.

20 AdemÆs,las ceras pueden ser ütiles solas o en combinaciOn con los materiales
mencionados antes, como excipientes para las realizaciones de matrices de liberación controlada de la presente invención. Los ejemplos no limitantes de Cstos incluyen cera blanca, parafina, cera microcristalina, cera carnauba y sus mezclas.

25 El agente lipófilo puede estar presente en una cantidad entre aproximadamente 5% y
aproximadamente 90% en peso de la forma farmacØutica de matriz de liberación
controlada, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el agente lipófilo esta presente en una cantidad entre aproximadamente 10%
y aproximadamente 85%, y en otras realizaciones entre aproximadamente 30% y
30 aproximadamente 60% en peso de la forma farmacØutica de matriz de liberación
controlada.

Los ejemplos no limitantes de polImeros hidrOfilos que se pueden usar en ciertas realizaciones de la forma farmacØutica de matriz de liberación controlada incluyen
35 hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), hidroxietilcelulosa
(HEC), carboximetilcelulosa (CMC) u otros Øteres de celulosa, polioxietileno, Æcido algInico, derivados del Æcidoacrilico como Æcidopoliacrilico, CARBOPOLTM, poilmero

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de polimetacrilato como EUDRAGITfi RL, RS, R, S, NE y E, polfmero del Æcido
acrilico, polimero del Æcidometacrflico, polImero del hidroxietil metacrilato (HEMA), poilmero de hidroximetil metacrilato (HMMA), alcoholes polivinilicos y sus mezclas.

5 El poilmero hidrófilo puede estar presente en una cantidad entre aproximadamente 10% y
aproximadamente 90% en peso de la forma farmacØutica de matriz de liberación
controlada, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci poilmero hidrófilo estÆpresente en una cantidad entre aproximadamente
20% y aproximadamente 75%, y en otras realizaciones entre aproximadamente 30% y
10 aproximadamente 60% en peso de la forma farmacØutica de matriz de liberación
controlada.

En al menos una realización, la forma farmacØutica de matriz de liberaciOn controlada comprende hidroxipropilmetilcelulosa (HPMC). Ejemplos no limitantes de
15 hidroxipropilmetilcelulosas que se pueden usar incluyen METHOCELfi E (tipo USP
2910), METHOCELfi F (tipo USP 2906), METHOCELfi J (tipo USP 1828), METHOCELfi K (tipo USP 220 1) y METHOCELfi serie 310, productos de The Dow Chemical Company, Midland, Mich., EE. UU. El grado promedio de sustitución con metoxilo en estos productos puede variar de aproximadamente 1,3 a aproximadamente
20 1,9, incluidos todos los valores y rangos intermedios (de las tres posiciones en cada
unidad del polImero de celulosa que estÆndisponibles para sustituciOn) mientras el grado promedio de sustitución con hidroxipropilo por unidad expresada en tØrminos molares
puede variar de aproximadamente 0,13 a aproximadamente 0,82, incluidos todos los
valores y rangos intermedios. La forma farn acØutica puede comprender los diferentes
025 grados de HPMC que tienen diferentes viscosidades. El tamaflo de un poilmero de
HPMC se expresa no como el peso molecular sino en tØrminos de su viscosidad como
una solución al 2% aproximadamente en peso en agua. Los diferentes grados de HPMC
se pueden combinar para lograr las caracterfsticas deseadas de viscosidad. Por ejemplo,
el al menos un poilmero farmacØuticamente aceptable puede comprender dos poilmeros
30 de HPMC como por ejemplo METHOCELfi K3 LV (que tiene una viscosidad de
aproximadamente 3 cp) y METHOCELfi Ki OOM CR (que tiene una viscosidad de aproximadamente 100.000 cp). AdemÆs,el polImero puede comprender dos formas hidroxipropilcelulosa como KLUCELfi LF y KLUCELfi EF. AdemÆs,el al menos ui-i poilmero puede comprender una mezcia de un KLUCELfi y un METFOCELfi.

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En al menos una reaiización la forma farmacØutica de matriz de liberación controlada comprende un óxido de polietileno (OPE). El óxido de polietileno es un poilmero lineal

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de Oxido de etileno sin sustituir. En ciertas realizaciones se usan los polimeros poli(Oxido
de etileno) que tienen viscosidad-pesos moleculares promedio de aproximadamente
100.000 daltons y mayores. Los ejemplos no limitantes de poli(óxido de etileno) que
estÆn comercialmente disponiblesincluyen: POLYOXfi NF, grado WSR coagulante,
5 peso molecular 5 millones; POLYOXfi grado WSR 301, peso molecular 4 millones;
POLYOXfi grado WSR 303, peso molecular 7 millones; POLYOXfi grado WSR N-
60K, peso molecular 2 millones; y sus mezclas. Estos polimeros particulares son
productos de Dow Chemical Company, Midland, Mich., EE. UU. Existen y asimismo se pueden usar otros ejemplos’de óxidos de polietileno. El peso molecular necesario Para el
10 OPE se puede obtener mezclando OPE de pesos moleculares diferentes que estÆn
disponibles comercialmente.

En al menos una realización de la forma farmacØutica de matriz de liberación controlada,

0 se combinan OPE y HPMC dentro de la misma matriz de liberación controlada. En
15 ciertas realizaciones, los poli(Oxido de etileno) tienen pesos moleculares que varlan de
aproximadamente 2.000.000 a aproximadamente 10.000.000 Da, incluidos todos los
valores y rangos intermedios. Por ejemplo, en al menos una realización los óxidos de
polietileno tienen pesos moleculares que varlan de aproximadamente 4.000.000 a aproximadamente 7.000.000 Da. En ciertas realizaciones los polimeros de HPMC tienen
20 una viscosidad dentro dl rango de aproximadamente 4.000 centipoises a
aproximadamente 200.000 centipoises. Por ejemplo, en al menos una realizaciOn los
polimeros de HPMC tienen una viscosidad entre aproximadamente 50.000 centipoises y aproximadamente 200.000 centipoises y en otras realizaciones entre aproximadamente

10 80.000 centipoises y aproximadamente 120.000 centipoises. Las cantidades relativas de
25 OPE y HPMC dentro de Ia matriz de liberaciOn controlada pueden variar dentro del
alcance de la invención. En al menos una realización la relación de pesos OPE:HPMC es
de aproximadamente 1:3 a aproximadamente 3:1, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones la relación de pesos OPE:HPMC es de aproximadamente 1:2 a aproximadamente 2:1. En cuanto a la cantidad total de polimero
30 con relación a toda la matriz, esto tambiØn puede variar y puede depender de la
concentraciOn de fÆrmacodeseada. En al menos una realización la cantidad total de

polImero en la matriz puede constituir de aproximadamente 15% a aproximadamente
90% en peso de la forma farmacºutica de matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones la cantidad total de polimero en la
35 matriz es de aproximadamente 20% a aproximadamente 75%, en otras realizaciones de
aproximadamente 30% a aproximadamente 60% y aun en otras realizaciones de

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aproximadamente 10% a aproximadamente 20% en peso de la forma farmacØutica de
matriz.

En al menos una realización de la invenciOn la forma farmacØutica de matriz de
5 liberación controlada comprende un poilmero hidrófobo como la etilcelulosa. La
viscosidad de la etilcelulosa Se puede seleccionar para influir en la velocidad de
liberación del fÆrmaco. En ciertas realizaciones hi etilcelulosa tiene una viscosidad de

aproximadamente 7 a aproximadamente 100 cP, incluidos todos los valores y rangos intermedios (cuando se mide como una solución a! 5% a 25°C en un viscosImetro
10 Ubbeiohde, usando un disolvente 80:20 tolueno:etanol). En ciertas realizaciones ci
poilmero hidrófobo puede constituir de aproximadamente 10% a aproximadamente 90%
en peso de la forma farmacØutica de matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en al menos una realización el polImero hidrófobo constituye
de aproximadamente 20% a aproximadamente 75% y en otras realizaciones de
15 aproximadamente 30% a aproximadamente 60% en peso de la forma farmacØutica de
matriz.

En al menos una realización de la invenciOn la forma farmacØutica de matriz de
liberación controlada comprende al menos un aglutinante. En ciertas realizaciones el
20 aglutinante es insoluble en agua. Los ejemplos de aglutinantes inciuyen aceite vegetal
hidrogenado, aceite de ricino, parafina, alcoholes alifÆticos superiores, ÆcidosalifÆticos superiores, ªcidos grasos de cadena larga, Østeres de Æcidos grasos, materiales similares a
cera como alcoholes grasos, Østeres de Æcidos grasos,gliceridos de Æcidos grasos, grasas hidrogenadas, hidrocarburos, ceras normales, Æeido esteÆrico,alcohol estearIlico,

1025 polImeros hidrófobos e hidrófilos que tienen esqueletos hidrocarbonados y sus mezclas.
Los ejernplos no limitantes de polimeros aglutinantes solubles en agua incluyen almidón modificado, gelatina, polivinilpirrolidona, derivados de celulosa (como por ejemplo hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa (HPC)), alcohol polivinIlico
y sus mezclas. En al menos una reaiización el aglutinante puede estar presente en una
30 cantidad de aproximadamente 0,1% a aproximadamente 20% en peso de la forma
farmacØutica de matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci aglutinante estÆ presente enuna cantidad entre aproximadamente
0,5% y aproximadamente 15%, y en otras realizaciones entre aproximadamente 2% y aproximadamente 10% en peso de la forma farmacØutica de matriz.
35
En al menos una realización de la invenciOn la forma farmacØutica de matriz de
liberación controlada comprende al menos un lubricante. Los ej emplos no limitantes de

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lubricantes incluyen Æcidoestearico, aceites vegetales hidrogenados (como aceite de
semilla de algodón hidrogenado (Sterotexfi), aceite de soja hidrogenado (STEROTEXfi HM) y aceite de soja hidrogenado y cera de ricino (STEROTEXfi K)), alcohol
estearilico, leucina, polietilenglicol (PM 1.450, adecuadamente 4.000 y mayor), estearato
5 de magnesio, monoestearato de glicerilo, ÆcidoesteÆrico,behenato de glicerilo,
polietilenglicol, polimeros de óxido de etileno (por ejemplo, CARBOWAXfi), lauril
sulfato de sodio, lauril sulfato de magnesio, oleato de sodio, estearil fumarato de sodio, DL-leucina, silice coloidal y sus mezclas. El lubricante puede estar presente en una
cantidad entre aproximadamente 0% y aproximadamente 4% en peso de la matriz sin
10 recubrir comprimida, incluidos todos los valores y rangos intermedios. Por ejemplo, en
ciertas realizaciones el lubricante estÆpresente en una cantidad entre aproximadamente
0% y aproximadamente 2,5% en peso de la matriz sin recubrir comprimida.

SEnal menos una realización de la invención la forma farmacØutica de matriz de
15 liberaciOn controlada comprende un plastificante. Los ejemplos no limitantes de
plastificantes incluyen sebacato de dibutilo, ftalato de dietilo, citrato de trietilo, citrato de tributilo, triacetina, Østeres del ÆcidocItrico como citrato de trietilo NF XVI, citrato de
tributilo, ftalato de dibutilo, 1,2-propilenglicol, polietilenglicoles, propilenglicol, ftalato
de dietilo, aceite de ricino, monoglicØridos acetilados, Østeres de ftalato y sus mezclas.
20 En al menos una realización el plastificante puede estar presente en una cantidad de
aproximadamente 1% a aproximadamente 70% en peso del polimero de liberación
controlada en a forma farmacØutica de la matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el plastificante estÆpresente en una

10 cantidad entre aproximadamente 5% y aproximadamente 50%, y en otras realizaciones
25 entre aproximadamente 10% y aproximadamente 40% en peso del polimero de liberaciOn
controlada en la forma farmacØutica de matriz.

En al menos una realización de la invención la forma farrnacØutica de matriz de
liberación controlada comprende al menos un diluyente, cuyos ejemplos no limitantes
30 incluyen fosfato dicälcico, sulfato de calcio, lactosa o sacarosa u otros disacÆridos,
celulosa, derivados de celulosa, caolin, manitol, almidón seco, glucosa u otros monosacaridos, dextriria ii otros polisacÆridos,sorbitol, inositol, sucralfato, hidroxiapatita cÆlcica,fosfatos de calcio, sales de Æcidograso como estearato de magnesio y sus mezclas. En ciertas realizaciones el diluyente se puede agregar en una cantidad para que
35 la combinación del diluyente y la sustancia activa comprenda hasta aproximadamente
60% y en otras realizaciones hasta aproximadamente 50%, en peso de la composición.

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En al menos una realización de la invención la forma farmacØutica de matriz de
liberación controlada comprende un solubilizante. El solubilizante puede actuar para aumentar la solubilidad instantÆneade la sal de bupropion. El solubilizante se puede seleccionar entre los tensioactivos hidrófilos o los tensioactivos lipOfilos o sus mezclas.
5 Los tensioactivos pueden ser tensioactivos aniónicos, no iónicos, catiónicos y
zwiteriónicos. Los tensioactivos hidrófilos no iónicos se pueden seleccionar del grupo compuesto, pero no exciusivamente, de: Østeres de Æcidosgrasos de polietilenglicol sorbitÆny productos hidrófilos de transesterificación de un poliol con al menos un miembro del grupo de los triglicØridos, los aceites vegetales y aceites vegetales
10 hidrogenados como glicerol, etilenglicol, polietilenglicol, sorbitol, propilenglicol,
pentaeritritol o un sacÆrido, d-a-tocoferilopolietilenglicol 1.000 succinato. Los tensioactivos ionicos se pueden seleccionar del grupo compuesto, pero no
exelusivamente, de: sales de alquilamonio; sales de Æcidofusidico; derivados de Æcidos grasos de aminoÆcidos,oligopeptidos y polipØptidos; derivados gliceridos de
15 aminoÆcidos, oligopØptidosy polipØptidos; lecitinas y lecitinas hidrogenadas;
lisolecitinas y lisolecitinas hidrogenadas; fosfolipidos y sus derivados; lisofosfoilpido y
sus derivados; sales de Østeres de Æeidosgrasos de camitina; sales de alquilsulfatos; sales
de Æcidos grasos; docusato de sodio;lactilatos de acilo; Østeres de Æcido tartrico monoy diacetilados de mono y diglicØridos; mono y diglicØridos succinilados; Østeres de Æcido
20 cItrico de mono y diglicØridos; y sus mezclas. Los tensioactivos lipOfilos se pueden
seleccionar del grupo compuesto, pero no exciusivamente, de: alcoholes grasos; Østeres
de Æcidosgrasos del glicerol; Østeres de ªcidos grasos de glicerol acetilado; Østeres de
Æcidos grasos de aleoholes inferiores; Østeres deÆcidosgrasos de propilenglicol; Østeres
de Æcidosgrasos de sorbitÆn; Østeresde Æcidosgrasos de polietilenglicol sorbitÆn;
1025 esteroles y derivados del esterol; esteroles y derivados del esterol polioxietilados; Øteres
aiqullicos de polietilenglicol; Østeres de azücares; Øteres de azücares; derivados del ªcido
lÆctico de monoy diglicØridos; productos hidrófobos de transesterificación de un poliol
con al menos un miembro del grupo de los gliceridos, aceites vegetales, açeites vegetales hidrogenados, Æcidosgrasos y esteroles; vitaminas liposolubles/derivados de vitaminas;
30 Østeres de Æcidos grasos dePEG sorbitÆn,Østeres de Æcidosgrasos de PEG glicerol,
Æcidosgrasos poliglicerizados, copoilmeros en bloque de polioxietileno-polioxipropileno, Østeres de Æcidos grasos de sorbitan;y sus mezelas. En al menos una realización ci solubilizante se puede seleccionar entre: estearato de PEG-20-glicerilo (por ejemplo, CAPMULfi de Abitec), aceite de ricino hidrogenado PEG-40 (por ejemplo,
35 CREMOPHOR RH 409 de BASF), aceite de mafz PEG-6 (por ejemplo, LABRAFIL(K
de Gattefosse), lauril macrogol 32 glicdrido (por ejemplo, GELUCIRE44/149 de
Qattefosse) estearoil macrogol glicØrido (por ejemplo, GELUCIRE50/139 de

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Gattefosse), mono dioleato de poliglicerilo 10 (por ejemplo, CAPROLfi PEG860 de Abitec), oleato de propilenglicol (por ejemplo, LUTROLfi de BASF), dioctanoato de propilenglicol (por ejemplo, CAPTEXfi de Abitec), caprilato/caprato de propilenglicol
(por ejemplo, LABRAFACfi de Gattefosse), monooleato de glicerilo (por ejemplo,
5 PECEOLfi de Gattefosse), monolinoleato de glicerol (por ejemplo, MAISINEfi de
Gattefosse), monoestearato de glicerol (por ejemplo, CAPMULfi de Abitec),
monolaurato de sorbitÆn PEG-20 (por ejemplo, TWEEN209 de Id), lauril Øter PEG-4
(por ejemplo. BRIJ309 de Id), diestearato de sacarosa (por ejemplo, SUCROESTER70
de Gattefosse), monopalmitato de sacarosa (par ejemplo, SUCROESTER1 5fi de
10 Gattefosse), copoilmero en bloque de polioxietileno-polioxipropileno (par ejemplo, serie
LUTROLfi de BASF), hidroxiestearato de polietilenglicol 660, (pot ejemplo,
SOLUTOLfi de BASF), lauril sulfato de sodio, dodecil sulfato de sodio, sulfosuccinato
de dioctilo, L-hidroxipropilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, alginato
de propilenglicol, taurocolato de sodio, glicocolato de sodio, desoxicolato de sodio,
15 betaInas, polietilenglicol (par ejemplo, CARBOWAXfi de DOW), d-a-tocoferil
polietilenglicol 1.000 succinato, (Vitamina E TPGSfi de Eastman) y sus mezelas. En al menos otra realización ci solubilizante se puede seleecionar entre aceite de ricino hidrogenado PEG-40 (par ejemplo, CREMOPHOR RH 409 de BASF), lauril macrogol-
32 glicrido (por ejemplo, GELUCIRE 44/149 de Gattefosse) estearoil macrogol
20 glicØrido (por ejemplo, GELUCIRE50/13fi de Gattefosse), monolaurato de sorbitÆn
PEG-20 (por ejemplo, TWEEN209 de ICI), lauril Øter PEG-4 (por ejemplo, BRIJ309 de
Id), copoilmero en bloque de polioxietileno-polioxipropileno (por ejemplo, serie
LUTROLfi de BASF), lauril sulfato de sodio, dodecil sulfato de sodio, polietilenglicol

S (por ejemplo, CARBOWAXfi de DOW) y sus mezclas.

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En al menos una realización de la invenciOn la forma farmacØutica de matriz de
liberación controlada comprende un potenciador del hinchamiento. Los potenciadores
del hinchamiento son integrantes de una categorIa de excipientes que Se hinchan
rÆpidamenteen gran medida y dan lugar a un aumento del tamano del comprimido. A
30 menores concentraciones, estos excipientes Se pueden usar como superdesintegrantes; sin
embargo a concentraciones por encima de 5% p/p estos agentes pueden actuar como potenciadores del hinchamiento y ayudar a aumentar el tamaflo de la forma farmacØutica
de matrjz. De acuerdo con ciertas realizaciones de las formas farmacØuticas de matriz de
la invención, los ejemplos de potenciadores del hinchamiento incluyen pero no
35 exciusivamente: hidroxipropilcelulosa poco sustituida, celulosa microcristalina,
carboximetilcelulosa sódica a cÆlcicareticulada, fibra de celulosa, polivinilpirrolidona reticulada, Æcidopoliacrilico reticulado, resina Amberlite reticulada, alginatos, silicato de

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magnesio-aluminio coloidal, grÆnulosde aimidón de maIz, grÆnulosde almidOn de arroz, granulos de almidón de papa, almidón pregelatinizado, carboximetil almidón sódico y sus mezclas. En al menos una realización de las fonnas farmacØuticas de matriz, el
potenciador de hinchamiento es polivinilpirrolidona reticulada. El contenido del
5 potenciador de hinchamiento puede ser de aproximadamente 5% a aproximadamente
90% en peso de la forma farmacØutica de matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el potenciador de hinchamiento estÆ presente en una cantidad entre aproximadamente 10% y aproximadamente 70%, y en
otras realizaciones entre aproximadamente 15% y aproximadamente 50% en peso de la
10 forma farmacºutica de matriz.

En al menos una realización de la invención la forma farmacØutica de matriz de
liberación controlada comprende aditivos para perinitir que el agua penetre en el nücleo
de la preparación (de aqul en adelante denominada "base hidrófila"). En ciertas
15 realizaciones, la cantidad de agua requerida para disolver 1 g de la base hidrófila no es
mÆsde aproximadamente 5 ml, y en otras realizaciones no es mÆs deaproximadamente 4
ml a la temperatura de aproximadamente 20°C + 5°C. Cuanto mayor la solubilidad de la base hidrófila en agua, mÆseficaz es la base en pernlitir que el agua penetre en el nücleo
de la preparación. La base hidrófila incluye, entre otros, polImeros hidrófilos como
20 polietilenglicol (PEG); (por ejemplo, PEG400, PEG1500, PEG4000, PEG6000 y
PEG20000, producido por Nippon Oils and Fats Co.) y polivinilpirrolidona (PVP); (por
ejemplo, PVP K30 de BASF), alcoholes de azücares como D-sorbitol, xilitol o similares, azücares como sacarosa, maltosa anhidra, D-fructosa, dextrano (por ejemplo, dextrano
40), glucosa o similares, tensioactivos como polioxietileno-aceite de ricino hidrogenado
025 (HCO; por ejemplo, CREMOPHORfi RH40 producido por BASF, HCO-40 y HCO-60
producido por Nikko Chemicals Co.), polioxietileno-polioxipropilenglicol (por ejemplo, PLURONICfi F68 producido por Asahi Denka Kogyo K.K.), Østeres de polioxietileno-sorbitÆnde Æcidos grasos dealto peso molecular (TWEEN(M; por ejemplo, TWEENfi80 producido por Kanto Kagaku K.K.) o similares; sales como cloruro de sodio, cloruro de
30 magnesio o similares; ÆcidosorgÆnicos como Æcido cItrico, Æcido tartÆricoo similares;
aminoÆcidoscomo glicina, f3-alanina, clorhidrato de lisina o similares; y amino azücares como meglumina. En al menos una realización la base hidrófila es PEG6000, PVP, D-sorbitol o sus mezclas.

35 En otra realizaciOn de la invenciOn la forma farmacØutica de matriz de liberaciOn
controlada comprende al menos un desintegrante. Los ejemplos no limitantes de desintegrantes para usar en la forma farmacØutica de matriz incluyen croscarmelosa

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sódica, crospovidona, Æcido alginico, alginato de sodio, Æcidometacrflico-DV13, PVP reticulada, celulosa microcristalina, polacriliria potÆsica, glicolato dealmidón sódico,
almidón, almidón pregelatinizado y sus mezclas. En al menos una realización el desintegrante se selecciona entre polivinilpirrolidona reticulada (por ejemplo,
5 KOLLIDON(g CL), carboximetilcelulosa sódica reticulada (por ejemplo, AC-DI-
SOLTM), almidón o derivados de almidón como glicolato de almidón sódico (por
ejemplo, EXPLOTABfi), o combinaciones con almidón (por ejemplo, PRIMOJELTM),
resinas de intercambio ionico hinchables, como AMBERLITETM IRP 88, formaldehIdo-
caselna (por ejemplo, ESMA SPRENGTM) y sus mezclas. En al menos una realización el
10 desintegrante es glicolato de almidón sódico. El desintegrante puede estar presente en
ciertas realizaciones en una cantidad de entre aproximadamente 0% a aproximadamente
20% del peso total de la matriz, incluidos todos los valores y rangos intermedios.

40 Las matrices de liberaciOn controlada de la presente invención pueden contener ademÆs
15 uno o mÆsexcipientes farmacØuticamente aceptables como, auxiliares o agentes de
granulación, colorantes, aromatizantes, ajustadores del pH, antiadherentes, deslizantes y excipientes similares convencionalmente usados en las composiciones farmacØuticas.

En al menos una realizaciOn de la invenciOn que comprende poilmeros hinchables con
20 agua formulados dentro de la matriz, la cinØtica de liberación de la sal bromhidrato de
bupropion desde la matriz depende de la magnitud relativa de la velocidad de
hinchamiento del polfmero en el frente móvil gomoso/vitreo y la velocidad de erosiOn del polimero en el frente de poilmero hinchado/medio de disolución. La cinØtica de
liberaciOn para la liberaciOn de la sal bronihidrato de bupropion desde la matriz se puede
25 aproximar con la ecuaciOn siguiente:
MtIMTktn
donde t es tiempo,
Mt es la cantidad de agente farmacØutico que se liberó en el tiempo t,
MT es la cantidad total de agente farmacØutico contenido en la matriz,
30 k es una constante y
n es el exponente de la cinØtica de liberación

Esta ecuaciOn es vÆlidasiempre que n siga siendo casi constante. Cuando n es igual a
uno, la liberaciOn del agente farmacØutico desde la matriz tiene una cinØtica de orden
35 cero. Entonces, la cantidad de agente farmacØutico liberado es directamente proporcional
al tiempo.

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Cuando el proceso de hinchamiento del poilmero elegido para ci excipiente es ci proceso principal que controla la iiberacióri del fÆrmaco (en comparación con la erosion del poilmero hinchado), puede resultar una cinØtica de liberaciOn de orden distinto de cero.
En general, estas cinØticas de liberación establecen un valor de n que se acerca a 0,5, conduciendo a cinØticas de liberaciOn del tipo Fickian de raIz cuadrada.

En al menos una reaiización de la invención, los poilmeros que se van a incluir en la formulación Se seleccionan.para lograr una cinØtica de orden cero. La cinØtica de
liberaciOn de la matriz tambiØn puede ser establecida por el agente farmacØutico mismo.
10 Un fªrmaco que es sumamente soluble (por ejemplo, bupropion) puede tender a ser
liberado mÆs rÆpido que los farmacos que tienen solubilidad baja.Cuando un fÆrmaco
tiene solubilidad alta, el hinchamiento y la erosion del poilmero tienen lugar rÆpidamente para mantener una cinØtica de iiberación de orden cero. Si el hinchamiento y la erosiOn tienen lugar demasiado lentamente, el proceso de hinchamiento del polImero es ci
15 proceso principal que controla la liberación del fÆrmaco(puesto que la droga difundirÆ
del poilmero hinchado antes de que el poilmero se erosione). En esta situación, puede
resultar una cinØtica de libºraciOn de orden distinto de cero. Como resultado, la administración de un agente farmacØutico muy soluble requiere un excipiente que se
hinche y erosione relativamente rÆpido. Usartal material para producir una matriz que
20 durarÆ 24 horaspuede requerir una matriz grande. Para superar esta dificuitad, se puede
usar una matriz con forma de rosquilla con un orificio en ci medio con un polimero que
hincha y erosiona menos rÆpidamente. Con una matriz como esa, ci area superficial de la
matriz aumenta a medida que la matriz se erosiona. Esto expone mÆs poilmero, dando
lugar a mÆs hinchamientoy erosion del poilmero a medida que la matriz encoge de
925 tamaflo. Este tipo de matriz tambiØn se puede usar con agentes farmacØutieos muy
altamente solubles para.mantener una cinØtica de liberaciOn de orden cero.

En al menos otra realización de la invenciOn, se puede lograr una cinØtica de liberación
de orden cero controlando. ci area superficial de la forma farmacØutica de matriz que Se
30 expone a la erosiOn. Cuando se permite que ci agua difunda en una composición de la
matriz polimØrica se obtiene una liberación de orden cero cuando la velocidad de
liberación es regida o controlada mediante erosiOn de un area superficial constante por
unidad de tiempo. Para asegurar que la erosion de la composiciOn de la matriz polimerica
sea ci mecanismo de liberÆción predominante, es iitti1 proporcionar una composiciOn de la
35 matriz polimØrica que tenga propiedades que aseguren que la velocidad de difusión del
agua en la composición de la matriz polimØrica se corresponde prÆcticamente con la velocidad de disoluciOn de la composición de la matriz polimØrica en ci medio acuoso.

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Por lo tanto, ajustando la naturaleza y la cantidad de constituyentes en la composición de
la matriz polimØrica se puede lograr un mecanismo de liberación de orden cero. Las composiciones empleadas se recubren de tal manera que at menos una superficie estÆ expuesta al medio acuoso y esta superficie tiene un area superficial prÆcticamente
5 constante o controlada durante la erosion. En el presente contexto area superficial
controlada se relaciona con un area superficial predeterniinada pronosticada
habitualmente a partir de la forma del recubrimiento del sistema de dosificación. Puede
tener una forma cilIndrica uniforme simple o la forma cilindrica puede tener uno o mÆs
extremos de secciOn decreciente para disminuir (o aumentar) ci perlodo de liberación
10 inicial. En consecuencia, estas realizaciones proporcionan un mØtodo para controlar la
liberación de una sal de bupropion en un medio acuoso mediante erosiOn de at menos una superficie de una composiciOn fannacØutica que comprende:
(i) una composicion de la matriz que comprende (a) un polimero o una mezcla de Spoilmeros, (b) una sal bromhidrato de bupropion y, opcionalmente, (c) uno o mds
15 excipientes farmacØuticamente aceptabies y
(ii) un recubrimiento que tiene al menos una abertura que expone una superficie de dicha
matriz; donde ci recubrimiento comprende: (a) un primer derivado de celulosa que tiene propiedades termoplasticas y que esprÆcticaxnente insolubleen el medio acuoso en ci que
se usarÆla composiciOn, y al menos uno de (b) un segundo derivado de celulosa que es
20 soluble o dispersable en agua, (c) opeionalmente un plastificante o (d) un relleno, donde
ci mØtodo comprende ajustar la concentraciOn y/o la naturaleza de los ingredientes que constituyen la composición de la matriz de tal manera que la velocidad de difusión del
medio acuoso en la composición de 1a matriz corresponda a 100% 130% como, por
ejemplo a 100% – 25%,100% – 20%,100% – 15% o 100% – 10%, o 100% de la
25 velocidad de disoluciOn de la composiciOn de la matriz para obtener una liberaciOn de
orden cero de at menos aproximadamente 60% p/p como, por ejemplo al menos aproximadamente 65% p/p, al menos aproximadamente 70% p/p, at menos aproximadamente 75% p/p, at menos aproximadamente 80% p/p, al menos aproximadamente 85% p/p, at menos aproximadamente 90% p/p, at menos
30 aproximadamente 95% p/p o al menos aproximadamente 97% a aproximadamente 98%
p/p de la sal bromhidrato de bupropion desde la composiciOn farmacØutica cuando se la somete a una prueba de disolución in vitro.

En al menos otra realización de la invenciOn, se acerca a una liberación del fÆrmacode
35 orden cero mediante ci uso de: (a) un nücleo de depOsito que comprende!a sal
bronihidrato de bupropion y que tiene forma geomØtrica definida, (b) una plataforma de soporte aplicada a dieho niicleo de depósito y que se caracteriza porque dicho nücleo de

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depOsito contiene, mezclado con la sal bromhidrato de bupropion, un material polimØrico con un grado alto de hinchamiento en contacto con agua o liquidos acuosos, un material polimØrico gelificable, donde dichos materiales polimØricos son reemplazables por un
ü nico material polimØrico que tiene propiedades tanto de hinchamiento como de
gelificación, y otros adyuvantes capaces de proporcionar Ia mezcla con caracterfsticas adecuadas para su compresión y para su entrada de agua, donde dicha plataforma de
soporte comprende un material polimØrico insoluble en lIquidos acuosos y recubre parcialmente dicho nÆcleo dedepósito.

10 Estas y otras caracterIsticas y ventajas del sistema de acuerdo con ciertas realizaciones de
la forma farmacØutica de matriz serÆnmÆsevidentes a partir de la descripción de las realizaciones de la invención que se indican de aqul en adelante a modo de ejeruplo no limitante. El nücleo de depósito se puede obtener en general mediante compresiOn de la mezela que contiene la sal bromhidrato de bupropion a una presión entre
15 aproximadamente 1.000 y aproximadamente 4.000 kg/cm2, ineluidos todos los valores y
rangos intermedios, para adquirir por lo tanto una forma geomØtrica definida. Los
materiales polimØricos que tienen un grado de hinchamiento alto en general pueden ser polImeros insolubles reticulados, mientras que los materiales polimØricos gelificables son solubles y pueden controlar la entrada de agua.
20

La plataforma de recubrimiento comprende un material polimØrico insoluble en agua y opcionalmente insoluble en lIquidos biologicos biodegradables y capaz de mantener sus caracterIsticas de impermeabilidad al menos hasta la transferencia completa de la sal bromhidrato de bupropion contenida en el nicleo de depósito. Se aplica a una parte de la
 5 superficie externa del nüeleo de depOsito elegida de modo de dirigir adecuadamente y
regular cuantitativamente la liberación de la sal bromhidrato de bupropion. A este
respecto, puesto que la plataforma de soporte es impermeable al agua, el material
polimØrico del nücleo de depósito en ciertas realizaciones puede hincharse solo en esa
porciOn del depósito no recubierta con la plataforma.
30

La plataforma de soporte se puede obtener comprimiendo materiales polimØricos preseleccionados sobre ci nücleo de depósito, sumergiendo ci nücleo de depOsito en una solución de dichos materiales polimØricos en los disolventes orgÆnicosnormales o pulverizando dichas soluciones. Los materiales polimØricos que se pueden usar para
35 preparar la plataforma de soporte se pueden elegir de la clase que comprende aerilatos,
celulosas y derivados como etilcelulosa, acetato-propionato de celulosa, polietilenos y rnetacrilatos y copolImeros del Æeidoacrilico, aleoholes polivinIlicos y sus mezelas. Esta

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platafornia puede tener un espesor de aproximadamente 2 mm (por ejemplo, si se aplica por compresión) a aproximadamente 10 micras (por ejemplo, si se aplica por pulverización o inmersiOn), incluidos todos los valores y rangos intermedios, y
comprende de aproximadamente 10% a aproximadamente 90% de la superficie total del sistema, incluidos todos los valores y rangos intermedios.

Un factor para el control de la liberaeión de la sal bromhidrato de bupropion es la
intensidad y la duración de la fuerza de hinchamiento desarrollada por los materiales polimØricos hinchables contenidos en el nicleo de depósito en contacto con lIquidos
10 acuosos. A este respecto, la energia para activar, ejecutar y regular la liberación de la sal
bromhidrato de bupropion se puede determinar mediante la fuerza de hinchamiento desarrollada en el nücleo de depósito cuando Øste entra en contacto con agua 0 con
liquidos biológicos. Dicha fuerza tiene una intensidad y duración que puede variar en relación con el tipo y la cantidad de los materiales polimØricos usados para formular el
15 depósito y estÆentre los limites que tienen un valor mÆximoque se produce en el caso de
un depósito que contiene principalmente el poilmero hinchable y un valor mInimo que se produce en el caso de un depOsito que contiene principalmente el polimero gelificable.
Dicho polimero hinchable puede estar presente en una cantidad entre aproximadamente
5% y aproximadamente 80% en peso, incluidos todos los valores y rangos intermedios, y
20 dieho polimero gelificable en una cantidad entre aproximadamente 10% y
aproximadamente 90% en peso, incluidos todos los valores y rangos intermedios, con
respecto a la mezcla que forma el nücleo de depOsito.

0 Un factor de control adicional es la geometria de la plataforma de soporte, que limita el
25 hinchamiento del depósito y dirige la emisión de material desde Øl. Dentro del alcance de
estas realizaciones es posible concebir muchos sistemas para la liberación controlada del bromhidrato de bupropion, que basan su operaciOn en la fuerza de hinchamiento y
difieren entre si pot el tipo de plataforma de soporte usada.

30 En al menos otra realización de la invención disefiada para lograr liberación de orden
cero de la sal bromhidrato de bupropion, la cinØtica de liberaciOn del fÆrmacodesde una matriz de liberaciOn controlada es regida por una combinación de poilmeros diferentes
con caracterIsticas de hinchamiento diferentes. MÆsespecificamente, primero la sal bromhidrato de bupropion se granula con o se encapsula en un polimero menos
35 hinchable, como una goma, a formar un grÆnulo. Este grªnulo se coloca en una matriz de
un polimero erosionable mÆs hinchable. El polimero erosionable mÆshinchable tiene un coeficiente de velocidad de difusión que es mayor que el coeficiente de velocidad de

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diftTsiOn del poilmero relativamente menos hinchable. Promediada durante todo el perlodo de liberación del fÆrmaco, lavelocidad de difusión para ci poilmero mÆs hinchable es mayor que la velocidad de difusión para el poilmero menos hinchable. Es esta diferencia general en las velocidades de difusión entre el primer y segundo poilmero
la que controla la velocidad de liberación del fÆrmaco yle permite al sistema acercarse a
una administraciOn del fÆrinacode orden cero durante el perlodo de liberación del
fÆrmaco. En al menos una realización, la pectina y la HPMC estan presentes como los poilmeros mÆs hinchables en relacionesde aproximadamente 2:7 a aproximadamente 4:5, incluidos todos los valores y rangos intermedios, y la gelatina estÆpresente como ci
10 polImero menos hinchable.

En al menos otra realización de la invención se proporciona una composición de la matriz
de iiberación controlada que comprende bromhidrato de bupropion incorporado dentro de
una matriz homogØnea que incluye cantidades eficaces de al menos dos poilmeros que
15 tienen caracterfsticas de humectabilidad opuestas, donde al menos se selecciona an
poilmero que demuestra una tendencia mÆsfuerte hacia la hidrofobicidad y se
seleccionan ci o los otros polImeros que demuestran una tendencia mÆs fuertehacia la hidrofilicidad. En al menos una realización ci poilmero que demuestra una tendencia mÆs fuerte hacia la hidrofobicidad es etilcelulosa (EC) en tanto que ci polImero que demuestra
20 una tendencia mÆsfuerte hacia la hidrofilicidad es hidroxietilcelulosa (HEC) yb
hidroxipropilmetilcelulosa (FIPMC). La composición y el dispositivo de la presente
invenciOn se pueden proporcionar como una matriz y se pueden recubrir opcionalmente
con un material de recubrimiento que evita ci efecto de brote y/o el efecto por ci consumo
de alimentos asociados con medicamentos ingeridos por via oral e imparte las
1025 caracterIsticas de "furtividad" gastrointestinales. Dc conformidad con al menos una
realización es un mØtodo para preparar un dispositivo para la liberación controlada de la
sal bromhidrato de bupropion, donde el mØtodo comprende mezclar ci bromhidrato de bupropion con aproximadamente 5% a aproximadamente 25% en peso del polimero
hidrófilo, incluidos todos los valores y rangos intermedios, y de aproximadamente 1% a
30 aproximadamente 25% en peso del polImero hidrófobo, incluidos todos los valores y
rangos intermedios, agregando excipientes farmacØuticos adecuados, agentes activos de superficie y lubricantes, granulando la mezcla con disolventes como ci alcohol
isopropilico, secando la mezcla granular, moliendo la mezcla seca, agregando de aproximadamente 5% a aproximadamente 70% en peso de etiiceluiosa, incluidos todos
35 los valores y rangos intermedios, agregando un lubricante y opcionalmente un deslizante
y comprimiendo los grÆnulosen forma de matrices. Las matrices se revisten

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opcionalmente con un revestimiento gastrointestinal o una pelicula de recubrimiento farmacØuticamente aceptable.

En otra realización de la presente invención, se proporciona una forma farmacØutica de
5 matriz hinchable en la cual la sal bromhidrato de bupropion se dispersa en una matriz
polimØrica que es hinchable con agua en vez de solamente hidrófila, que tiene una
velocidad de erosion que es sustancialmente mÆs lenta quesu velocidad de hinchamiento
y que libera la sal bromhidrato de bupropion principalmente por difusión. La velocidad
de difusión de la sal brornhidrato de bupropion fuera de la matriz hinchable se puede
10 ralentizar aumentando el tamaflo de la partIcula de fÆrmaco,mediante la elecciOn del
polimero usado en la matriz, y/o mediante la elección del peso molecular del polimero.
La matriz hinchable estÆ compuesta deun polfmero de peso molecular relativarnente alto que se hincha con la ingestiOn. En al menos una realización la matriz hinchable aumenta
con la ingestion hasta un tamaflo que es al menos dos veces su volumen sin hincharse, y
15 eso promueve la retenciOn gÆstrieadurante la modalidad con alimentos. Al hincharse, la
matriz hinchable tambiØn se puede convertir durante un perfodo prolongado de un
polimero vItreo en un polimero que es gomoso en consistencia, o de un polimero
cristalino a uno gomoso. El lIquido penetrante causa despuØs la liberación de la sal bromhidrato de bupropion de manera gradual y prolongada mediante el proceso de
20 difusiOn de la solución, es decir, la disoluciOn de la sal bromhidrato de bupropion en el
lIquido penetrante y la difusiOn de la sal bromhidrato de bupropion disuelta fuera de la matriz hinchable. La matriz hinchable en sí es sOlida antes de la administración y, una
vez administrada, permanece sin disolverse en (es decir, no es erosionada por) el lIquido gÆstricodurante un perfodo suficiente para permitirle a la mayor parte de la sal
25 bromhidrato de bupropion ser liberada por el proceso de difusiOn de la solución durante
la modalidad con alimentos. El factor que limita la velocidad en la liberaciOn de la sal bromhidrato de bupropion de la matriz hinchable es por consiguiente la difusión
controlada de la sal bromhidrato de bupropion de la matriz hinchable en lugar de la
erosion, la disoluciOn o la descomposición quimica de la matriz hinchable.
30

Como tal, ci hinchamiento de la matriz polimØrica puede lograr al menos los siguientes objetivos: (i) torna la matriz suficientemente grande para provocar retención en el
estómago durante la modalidad con alimentos; (ii) localiza la iiberación del fÆrmacoen ci estOmago y el intestino delgado de modo que el fÆrmacotendrÆsu efecto total sin
35 degradacion colOnica, inactivación, o perdida de la biodisponibilidad; (iii) retrasa la
velocidad de difusiOn del fârmaco ci tiempo suficiente para proporcionar la
administraciOn multihora, controlada del fÆrmacoen, el estOmago.

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La sal bromhidrato de bupropion en la matriz hinchable puede estar presente en una cantidad eficaz entre aproximadamente 0,1% y aproximadamente 99% en peso de la
matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas
5 realizaciones el bromhidrato de bupropion estÆ presenteen la matriz hinchable en una
cantidad entre aproximadamente 0,1% y aproximadamente 90%, en otras realizaciones
entre aproximadamente 5% y aproximadamente 90%, aun en otras realizaciones entre aproximadamente 10% y aproximadamente 80% y en todavIa otras realizaciones entre aproximadamente 25% y Æproximadamente80% en peso de la matriz hinchable.
10

El poilmero hinchable en agua que forma la matriz hinchable de conformidad con estas realizaciones de la presente invención puede ser cualquier poilmero atóxico, que Se
hinche de una manera dimensionalmente irrestricta al embeberse en agua y que asegure
una liberación modificada de la sal bromhidrato de bupropion. Los ejemplos no
15 limitantes de los polImeros adecuados para usar en la matriz hinchable incluyen
poilmeros de celulosa y sus derivados (como por ej emplo; hidroxietilcelulosa, hidroxipropilcelulosa, carboximetilcelulosa y celulosa microcristalina, polisacÆridosy sus derivados, óxidos de polialquileno, polietilenglicoles, quitosana, poli(alcohol vinflico),
goma xantano, copoilmeros del anhidrido maleico, poli(vinilpirrolidona), almidón y
20 polImeros a base de almidón, poli(2-etil-2-oxazolina), poli(etilenimina), hidrogeles de
poliuretano y Æcidos poliacrilicosreticulados y sus derivados y sus mezclas. Otros
ejemplos incluyen copolfmeros de los poilmeros mencionados en la oraciOn anterior, incluidos copolImeros en bloque y polimeros injertados. Ejemplos especificos de
copolImeros incluyen PLURONICfi y TECTONICfi, que son copolImeros en bloque de
1025 óxido de polietileno-óxido de polipropileno.

Los tØrminos "celulosa" y "ceiulósico", como se usan en esta sección con respecto a las realizaciones de matriz hinchable de la presente invención, pueden denotar un poilmero
lineal de anhidroglucosa. Los ejemplos no limitantes de los poilmeros celulósicos
30 incluyen polimeros celulósicos aiquil sustituidos que se disuelven en ültimo tØrmino en el
tubo digestivo (01) de una manera predeciblemente retardada. En ciertas realizaciones
los derivados de celulosa aiquil sustituidos son los sustituidos con grupos alquilo de 1 a 3 Ætomosde carbono cada uno. Los ejemplos no limitantes incluyen metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa,
35 hidroxipropilmetilcelulosa, carboximetilcelulosa y sus mezclas. En cuanto a sus
viscosidades, una clase de celulosas aiquil sustituidas incluye aquellas cuya viscosidad
estÆ dentro del rango de aproximadamente 100a aproximadamente 110.000 centipoises

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como una soluciOn acuosa al 2% a 20°C. Otra clase incluye aquellas cuya viscosidad estÆ dentro del rango de aproximadamente 1.000 a aproximadamente 4.000 centipoises como
una solucióri acuosa al 1% a 20°C. En ciertas realizaciones las celulosas alquil
sustituidas son hidroxietilcelulosa e hidroxipropilmetilcelulosa. En al menos una
5 realización la hidroxietilcelulosa es NATRASOLfi 250HX NF.

Los óxidos de polialquileno que se pueden usar en ciertas realizaciones de las matrices hinchables incluyen los que tienen las propiedades descritas antes para los pollineros de celulosa alquil sustituidos. En al menos una realizaciOn el óxido de polialquileno es
10 poli(óxido de etileno), tØrmino que se usa aqul para denotar un polimero lineal de óxido
de etileno sin sustituir. En al menos una realización los polImeros de poli(óxido de
etileno) tienen pesos moleculares de aproximadamente 4.000.000 y mayores. Por
ejemplo, en cierta realización los polImeros de poli(óxido de etileno) tienen pesos moleculares dentro del rango de aproximadamente 4.500.000 a aproximadamente
15 10.000.000, incluidos todos los valores y rangos intermedios, y en otras realizaciones
tienen pesos moleculares dentro del rano de aproximadamente 5.000.000 a aproximadamente 8.000.000. En ciertas realizaciones los poli(óxido de etileno) son los
que tienen un peso molecular promedio dentro del rango de aproximadamente 1 x 105 a aproximadamente 1 x 107, y en otras realizaciones dentro del rango de aproximadamente
20 9 x 105 a aproximadamente 8 x 106. Los poli(óxido de etileno) a menudo se caracterizan
por su viscosidad en solución. Por ejemplo, en ciertas realizaciones los poli(óxido de
etileno) tienen una viscosidad en el rango de aproximadamente 50 a aproximadamente 2.000.000 centipoises para una solución acuosa a! 2 % a 20°C. En al menos una
realización ci poli(óxido de etileno) es uno o mÆs de losPOLYOXfi NF, grado WSR
25 Coagulante, peso molecular 5 millones y grado WSR 303, peso molecular 7 millones.
Sus mezclas son factibles.

Las gomas de poiisacÆrido,tanto naturales como modificadas (semisintØticas) se pueden
usar en las realizaciones de matriz hinchable de la presente invención. Los ej emplos no
30 limitantes incluyen dextrano, goma xantano, goma gelano, goma welano, goma rhamsano
y sus mezclas. En al menos una realizaciOn la goma de polisacÆridoes goma xantano.

Los Æcidospoliacrflicos reticulados que se pueden usar en las matrices hinchables de la presente invención incluyen aquellos cuyas propiedades son las mismas que las descritas
35 antes para la celulosa alquil sustituida y los polimcros de óxido de polialquileno. En
ciertas realizaciones los ªcidos poliacrflicos reticulados son los que tienen una viscosidad
que van a de aproximadamente 4.000 a aproximadamente 40.000 centipoises para una

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solueión acuosa al 1% a 25°C. Los ejemplos no limitantes de los Æcidospoliacrilicos reticulados adecuados incluyen CARBOPOLfi NF grados 971P, 974P y 934P. Otros ejemplos de ÆcidospoliacrIlicos reticulados adecuados incluyen polImeros conocidos
como WATER LOCKfi, que son copoilmeros de almidónlacrilatos/acrilamida.
5

La hidrofihicidad e hinchabilidad en agua de estos polimeros pueden hacer que las
matrices hinchables que contienen fÆrmaco aumenten de tamaflo en lacavidad gÆstrica debido al ingreso de agua para lograr un tamaflo que se pueda retener en el estOmago
cuando se introduzcan durante la modalidad con alimentos. Estas cualidades tambiØn
10 hacen que las matrices hinchables se tornen resbaladizas, lo que proporciona resistencia
al peristaltismo y ademÆs promuevesu retención en el estómago. La velocidad de
liberación del fÆrmaco de la matriz hinchable depende principalmente de la velocidad de imbibición en agua y la velocidad a la cual of fÆrmaco sedisuelve y se difunde del
polImero hinchado, que a su vez estÆ relacionada con la concentración de fÆrmaco en la
15 matriz hinchable. AdemÆs,debido a que estos poilmeros se disuelven muy lentamente en
el lIquido gªstrico, la matriz hinchable mantiene su integridad fisica durante al menos un periodo considerable, por ejemplo en muchos casos durante al menos aproximadamente
90% y en ciertas realizaciones, durante aproximadamente el 100% del perfodo de
dosificación. DespuØs las partIculas se disolverÆn lentamente o se descompondrÆn.La
20 disolución o descomposición total puede no ocurrir hasta aproximadamente 24 horas o
mÆsdespuØs que cesa el perfodo de dosificación concebido, aunque en la mayorIa de los
casos, la disolución o la descomposicion total ocurrirÆen las aproximadamente 10 a aproximadamente 24 horas siguientes al perlodo de dosificación.

025 La cantidad de polImero en relación con el fÆrmaco puede variar, dependiendo de la
velocidad de liberación del fÆrmaco deseaday del polImero, su peso molecular y los
excipientes que pueden estar presentes en la fonnulación. La cantidad de poilmero serÆ generalmente suficiente para retener al menos aproximadamente 40% del fÆrmaco dentro
de la matriz hinchable aproximadamente una hora despuds de la ingestion (o inmersiOn
30 en el lIquido gÆstrico). Enciertas realizaciones, la cantidad de polImero es tal que al
menos aproximadamente 50% del fÆrmaco permanece en la matriz aproximadamenteuna hora despuØs de la ingestion; en otras realizaciones al menos aproximadamente 60%, y
aun en otras realizaciones al menos aproximadamente 80%, del fÆrmaco permaneceen la matriz hinchable aproximadamente una hora despuØs de la ingestion. En ciertas
35 realizaciones el fÆrmaco serÆliberado casi completamente de la matriz hinchable en ci
transcurso de aproximadamente 10 horas; y en otras realizaciones en el transcurso de aproximadamente 8 horas, despuØs que la ingestion y la matriz polimØrica permanecerª

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prÆcticamenteintacta hasta que todo ci fÆrmaco selibera. En otras realizaciones, la cantidad de polimero seth tal que despuØs de aproximadamente 2 horas se libera no mÆs
de aproximadamente 40%, despuØs de aproximadamente 4 horas se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas se
5 libera al menos aproximadamente 75% y despuØs de aproximadamente 16 horas se libera
al menos aproximadamente 85%. El tØrmino "prÆcticamenteintacta" se usa aquf para
indicar una matriz pOlimØrica en la cual la porciôn de polimero conserva prÆcticamente
su tamafio y forma sin deterioro debido a que se solubiliza en ci lfquido gÆstrico o debido
a que se rompe en fragmentos o partIeulas pequenas.
10

En otras realizaciones de ejemplo la matriz hinchable liberarÆdespuØs de
aproximadamente 2 horas no mÆsde aproximadamente 40% de bromhidrato de
bupropion, despuØs de aproximadamente 4 horas de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas al menos aproximadamente
15 75% y despues que aproximadamente 16 horas al menos aproximadamente 85%.

Los polImeros hinchables en agua de las matrices hinchables se pueden usar
individualmente o en combinación. Ciertas combinaciones proporcionarÆn a menudo una liberación mÆscontrolada del fÆrmacoque sus componentes cuando se usan
20 individualmente. Los ejemplos incluyen polimeros a base de celulosa combinados con
gomas, como hidroxietilcelulosa o hidroxipropilcelulosa combinadas con goma xantano.
Otro ejemplo es poli(óxido de etileno) combinado con goma xantano.

Los beneficios de ciertas realizaciones de esta invención se pueden lograr en una gama
25 amplia de concentraciones del fÆrmacoy niveles de polimero, con la relación de pesos
entre fÆrmacoy polimero variando en general de aproximadamente 0,01:99,99 a aproximadamente 80:20, incluidos todos los valores y rangos intermedios. Por ejemplo,
en ciertas realizaciones las concentraciones del fÆrmaco (expresadasen tØrminos de porcentaje de peso del fÆrmacoen relación con ci total de fÆrmacoy polimero) estªn
30 dentro del rango de aproximadamente 15% a aproximadamente 80%, incluidos todos los
valores y rangos intermedios; en otras realizaciones dentro del rango de
aproximadamente 30% a aproximadamente 80%, incluidos todos los valores y rangos intermedios; y aun en otras realizaciones dentro del rango de aproximadamente 30% a aproximadamente 70%, incluidos todos los valores y rangos intermedios. En al menos
35 una realizaciOn la concentración de fÆrmaco estÆdentro del rango de aproximadamente
0,01% a aproximadamente 80%, incluidos todos los valores y rangos intermedios, y en al menos otra realización de aproximadamente 15% a aproximadarnente 80%, incluidos

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todos los valores y rangos intermedios. En al menos una realización la relación de pesos entre brornhidrato de bupropion y polimero en la matriz hinchable es d
aproximadamente 15:85 a aproximadamente 80:20, incluidos todos los valores y rangos intermedios.
5

Las formulaciones de las matrices hinchables de la presente invención pueden adquirir la forma de micropartleulas, comprimidos o microparticulas retenidas en cÆpsulas. En al menos una realización la formulación comprende micropartleulas consolidadas en una
masa compactada para la ingestion, aunque la masa compactada se separarÆen partIculas
10 individuales despuØs de la ingestiOn. Se pueden usar los mØtodos convencionales para
consolidar las micropartleulas de esta manera. Por ejemplo, las micropartleulas se
pueden colocar en cÆpsulas de gelatina conocidas en ci area como cÆpsulas "rellenas
duras" y cÆpsulas "blandas elÆsticas".Las composiciones de estas cÆpsulasy los procedimientos para llenarlas son conocidos por los tØcnicos con experiencia en la
15 formulaeión de fÆrmacos y su fabrieaciOn. El material de encapsulado debe ser muy
soluble para que las partIculas se liberen y se dispersen rÆpidamente en el estOmago
despuØs de la ingestion de la cÆpsula.

En ciertas realizaciones de las matrices hinchables de la presente invenciOn, la
20 formulación contiene una cantidad adicional de sal bromhidrato de bupropion u otro
fÆrmaco aplicadacomo Un recubrimiento que se disuelve rÆpidamenteen la parte exterior
de la micropartIcula o el comprimido. Este recubrimiento se denomina "dosis inicial" y
se incluye para la liberación inmediata en la circulaeión sangulnea del receptor despuØs
de la ingestion de la fomiulaciOn sin experimentar primero el proceso de difusión por el
025 que el resto del fÆrmaco dela formulaciOn debe pasar antes de ser liberado. La "dosis
inicial" puede ser lo suficientemente alta para elevar rÆpidamentela concentración
sangulnea de la droga pero no lo bastante alta como para producir la sobredosis
transitoria que es caracterIstica de formas farmacØuticas de liberaciOn inmediata que no estÆnformuladas de conformidad con esta invenciOn.
30

En al menos una realización de las matrices hinchables de la presente invenciOn, la forma farmacØutica es una cÆpsula de gelatina de tamafio0 que contiene o dos o tres pelets de polimero impregnado de fÆrniaco. Para las cÆpsulas de dos pelets, lospelets tienen forma cilindrica, de aproximadamente 6,6 mm o aproximadamente 6,7 mm de diÆmetro(o mÆs
35 generalmente, de aproximadamente 6,5 mm a aproximadamente 7 mm de diÆmetro,
incluidos todos los valores y rangos intermedios) y aproximadamente 9,5 mm o aproximadamente 10,25 mm de longitud (o mÆs generaimente,de aproximadamente 9

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mm a aproximadamente 12 mm de longitud, incluidos todos los valores y rangos
intermedios). Para las cÆpsulasde tres pelets, los pelets tienen nuevamente forma
cilIndrica, aproximadamente 6,6 mm de diÆmetroy aproximadamente 7 mm de longitud.
Para una cÆpsula degelatina de tamaflo 00 con dos pelets, los pelets son cilIndricos, de
5 aproximadamente 7,5 mm de diÆmetroy aproximadamente 11,25 mm de longitud. Para
una cÆpsula degelatina de tamaflo 00 con tres pelets, los pelets son cilmndricos, de aproximadamente 7,5 mm de diªmetro y aproximadamente 7,5 mm de longitud. En al menos otra realización, la forma farmacØutica es un ünico comprimido, alargado, con dimensiones de aproximadamente 18 mm a aproximadamente 22 mm de longitud,
10 incluidos todos los valores y rangos intermedios, de aproximadamente 6,5 mm a
aproximadamente 10 mm de ancho, incluidos todos los valores y rangos intermedios, y
de aproximadamente 5 mm a aproximadamente 7,5 mm de altura, incluidos todos los
valores y rangos intermedios. En al menos otra realizaciOn, la forma farmacØutica es un Sünico comprimido, alargado, con dimensiones de aproximadamente 18 mm a
15 aproximadamente 22 mm de longitud, incluidos todos los valores y rangos intermedios,
de aproximadamente 6,5 mm a aproximadamente 7,8 mm de ancho, incluidos todos los valores y rangos intermedios, y de aproximadamente 6,2 mm a aproximadamente 7,5 mm
de altura, incluidos todos los valores y rangos intermedios. En al menos una realización
las dimensiones son aproximadamente 20 mm de longitud, aproximadamente 6,7 mm de
20 ancho y aproximadamente 6,4 mm de altura. Estos son sOlo ejemplos; las formas y los
tamaæosse pueden variar considerablemente.

En ciertas realizaciones, la matriz que contiene bromhidrato de bupropion se puede
realizar de acuerdo con cualquiera de los mØtodos descritos en el presente.

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La mezcla particulada frmaco/polimero o la matriz de polimero hinchable impregnada
de fÆrmacode ciertas realizaciones se pueden preparar mediante diversas tcnicas convencionales de mezela, trituración y fabricaciOn fÆcilmenteevidentes para los
tØcnicos capacitados en la qulmica de las formulaciones de fÆrmacos.Los ejemplos de
30 tales tØcnicas incluyen: (1) Compresión directa, usando punzones y matrices apropiados,
como los comercializados por Elizabeth Carbide Die Company, Inc., McKeesport, Pa.,
EE. UU.; los punzones y las matrices se ajustan a una compresora rotatoria adecuada,
como la compresora automÆticaElizabeth-Hata single-sided Hata Auto Press, con 15, 18
o 22 estaciones y que se puede adquirir a Elizabeth-Hata Internacional, Inc., North
35 Huntington, Pa., EE. UU.; (2) InyecciOn o moldeado por compresión usando los moldes
adecuados instalados en una unidad de compresión, como las que comercializa Cincinnati Milacron, Plastics Machinery Division, Batavia, Ohio, EE. UU.; (3) Granulación seguida

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de compresión; y (4) Extrusion en forma de una pasta, en un molde o de un extrudado
para cortar en trozos.

En cuanto a las matrices hinchables de ciertas realizaciones de la presente invención,
5 cuando las micropartIculas se elaboran mediante compresión directa, la adición de
lubricantes puede ser ütil y, en ciertas realizaciones, conveniente para promover el fluj o
del polvo y para evitar el decapado de la micropartIcula (ruptura de una porciOn de la partIcula) cuando se reduce la presión. Los ejemplos no limitantes de los lubricantes adecuados incluyen estearato de magnesio (en una concentración entre aproximadamente
10 0,25% y aproximadamente 3% en peso, incluidos todos los valores y rangos intermedios,
y en ciertas realizaciones en menos de aproximadamente 1% en peso, en la mezela de
polvo), y aceite vegetal hidrogenado (en ciertas realizaciones trigliceridos hidrogenados y refinados de los ªcidos esteÆrico y palmItico en aproximadamente 1% a
aproximadamente 5% en peso, incluidos todos los valores y rangos intermedios, por
15 ejemplo en al menos una realizaciOn en aproximadamente 2% en peso). Se pueden
agregar otros excipientes para mejorar la capacidad de fluir del polvo y reducir la
adherencia.

Ciertas realizaciones de las matrices hinchables de la presente invención pueden ser de
20 utilidad cuando se las administra a un sujeto que estÆ enel estado digestivo (tambiØn
denominado modalidad posprandial o "con alimentos"). La modalidad posprandial es distinguible de la modalidad interdigestiva (o "en ayunas") por sus patrones diferentes de actividad motora gastroduodenal, que determinan el tiempo de retenciOn gÆstrica o de trÆnsitogÆstrico delcontenido del estómago.
 25

Las matrices de liberación controlada de ciertas realizaciones de la presente invención se pueden preparar mediante mØtodos conocidos en el area. Un ejemplo de un mØtodo de fabricaciOn de matrices de IiberaciOn controlada es la extrusion por fusion de una mezcla
que contiene la sal de bupropion, el o los polImeros hidrófobos, el o los poilmeros
30 hidrOfilos y opcionalmente un aglutinante, un plastificante y otros excipientes como los
descritos precedentemente. Otros ejemplos de mØtodos de fabricación de matrices de liberación controlada incluyen granulación hümeda, granulaciOn seca (por ejemplo, aglutinacion, compactación con rodillos), compresión directa, granulacion por fusion y granulaciOn rotatoria.
35

Ademªs, las partIculas de liberaciOn controlada que se pueden comprimir o colocar en las cÆpsulasse pueden producir combinando la sal bromhidrato de bupropion y un

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componente fundible hidrófobo y/o un diluyente, opcionalmente con un agente que modifique la liberación incluidos un material fundible soluble en agua o un particulado soluble o un material orgÆnicoo inorgÆnicoinsoluble. Los ejemplos de los posibles componentes fundibles hidrófobos incluyen materiales hidrófobos como ceras o aceites
5 naturales o sintØticos (por ejemplo, aceite vegetal hidrogenado, aceite de ricino
hidrogenado, cera microcristalina, Cera de Abeja, cera carnauba y monoestearato de glicerilo). En al menos una realización el componente fundible hidrófobo tiene un punto
de fusion de aproximadamente 35°C a aproximadamente 140°C, incluidos todos los
valores y rangos intermedios. Los ejemplos de agentes que modifican la liberaciOn
10 incluyen polietilenglicol y materiales particulados como fosfato dicÆlcicoy lactosa.

En ciertas realizaciones, las matrices de liberaciOn controlada se pueden producir
trabajando mecÆnicamenteuna mezcla de una sal bromhidrato de bupropion, un
componente fundible hidrOfobo, y opcionalmente un componente de liberación incluido
15 un material fundible soluble en agua 0 un material particulado orgÆnico0 inorgÆnico
soluble o insoluble en condiciones de mezcla que produzca aglomerados, rompiendo los aglomerados para producir iniciadores de la liberaciOn controlada que tengan las
propiedades de liberación deseadas; y opcionalmente agregando mªs vehIculo 0 diluyente
y repitiendo los pasos de mezcla hasta que se obtengan los iniciadores de la liberación
20 controlada con propiedades de liberación deseadas. Estas particulas tambiØn se pueden
separar por tamafio (por ejemplo, tamizando y encapsulando en cÆpsulaso comprimiendo
en forma de matriz).

La cantidad de material fundible hidrOfobo usado en los mØtodos mencionados antes
25 puede variar de aproximadamente 10% a aproximadamente 90% en peso, incluidos todos
los valores y rangos intermedios. Los mezcladores ütiles en dichos mØtodos son
conocidos e incluyen los mezcladores convencionales de gran velocidad con interiores de acero inoxidable. Por ejemplo, se puede procesar una mezcla hasta que se produce una temperatura del lecho de aproximadamente 40°C o mayor y la mezcla logra una textura
30 granular cohesiva que comprende los tamafios deseados de partIcula.

Segün se observa si la mezcla contiene aglomerados, Østos se pueden romper usando
mØtodos convencionales para producir una mezcla de polvo y particulas del tamafio
deseado que se pueden separar por tamaæo usando un cedazo, tamiz o malla del tamaflo
35 apropiado. Este material puede ser devuelto a un mezclador de gran velocidad y
procesado aün mÆs segin sedesee hasta que los materiales fundibles hidrófobos
empiecen a ablandarse/fundirse y opcionalmente Se puede agregar mÆsmaterial

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hidrófobo y seguir mezclando hasta que se obtengan particulas con el rango de tamaæo deseado. Aün mÆs, las particulas que contienen sal bromhidrato de bupropion se pueden producir mediante el proceso de fusion conocido en ci area y combinar en eÆpsulaso comprimir en forma de matrices.

Estas particulas se pueden combinar con uno o ma’s excipientes como diluyentes,
lubricantes, aglutinantes, auxiliares de fiujo, desintegrantes, agentes que actüan en la superficie, materiaies solubies en agua, colorantes y similares.

10 AdemÆs, las matricesde liberaciOn controlada se pueden recubrir opcionaimente con uno
o mÆsrecubrimientos funcionales o no funcionales usando mØtodos de recubrimiento conocidos. Los ej emplos de recubrimientos pueden inciuir ci recubrimiento de liberación controlada XL y el recubrimiento de matriz EA descritos aqul, que pueden controiar ademÆsla liberación de la sal bromhidrato de bupropion y/o de otro fÆrmaco.
15

En at menos una realizaeión, las matrices de liberación controlada pueden recubrirse cada
una con at menos un recubrimiento que enmascara ci sabor. El recubrimiento que
enmascara el sabor puede emnascarar el sabor de la sal bromhidrato de bupropion en las matrices. En at menos una realizaciOn las formulaciones de recubrimiento que enmascara
20 ci sabor contienen ingredientes polimØricos. Se contempla que se pueden usar en ci
recubrimiento otros excipientes compatibles con los objetivos de la presente invenciOn
que enmascaran ci sabor.

En at menos una realizaciOn de la forma farmacØutica de matriz, el recubrimiento que
25 enmascara ci sabor comprende un poilmero como etilcelulosa, que se puede usar como un
poilmero seco (como ETHOCEL) solubilizado en ci disolvente orgÆnico antesde usar, o como una dispersion acuosa. Una dispersion acuosa comercialmente disponible de etilcelulosa es AQUACOATfi. El AQUACOATfi se puede preparar disoiviendo la etilcelulosa en un disolvente orgÆnicoinmiscible con agua y luego emulsificar ci mismo
30 en agua en presencia de un tensioactivo y un estabilizador. DespuØs de la
homogeneizacian para generar gotitas submicrónicas, ci disolvente orgÆnicose evapora
at vaclo para formar un pseudoiÆtex. El plastificante no se incorpora en el pseudolÆtex durante la fase de fabricación. Por to tanto, antes de usar el mismo como un
recubrimiento, ci Aquacoat se mezcla Intimarnente con un plastificante, adecuado antes de
35 usar. Otra dispersion acuosa de etilcelulosa se comercializa como SURELEASEfi. Este
producto se puede preparar incorporando un plastificante en la dispersion durante ci
proceso de fabricación. Se prepara una masa fundida cÆiientede un polimero, un

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plastificante (por ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, Æcido oleico) como una mezela homogenea, que luego se diluye eon una solución alealina para obtener una dispersion acuosa que se puede aplicar directamente sobre los sustratos.

5 En otras realizaciones de la forma farmacØutica de matriz, se pueden emplear poilmeros
polimetacrilato acrIlicos como poilmeros enmasearadores del sabor. En al menos una reaiizaeión, el recubrimiento que enmascara ci sabor es una laca de resina acrIlica usada
en forma de una dispersion acuosa, como EUDRAGITfi o KOLLICOATfi. En otras realizaciones, ci recubrimiento acrIlico comprende una mezela de dos lacas de resina
10 acrilicas, EUDRAGITfi RL y EUDRAGITfi RS, respectivamente. EUDRAGITfi RL y
EUDRAGITfi RS son copolimeros de Østeres acrilicos y metacrIlicos con un contenido
bajo de grupos amonio cuaternario, la relaeiOn molar entre los grupos amonio y los
restantes Østeres (rnet)acrflicos neutros es de 1:20 en EUDRAGITfi RL y 1:40 en EUDRAGITfi RS. El peso molecular medio es 150.000. Las designaciones del eOdigo
15 RL (permeabilidad alta) y IS (permeabilidad baja) se refieren a las propiedades de
permeabilidad de estos agentes. Las mezclas EUDRAGITfi RL/RS son insolubles en
agua y en los liquidos digestivos. Sin embargo, los recubrimientos elaborados a partir de ellos son hinchables y permeables en soluciones acuosas y lIquidos digestivos. Las dispersiones o soluciones de EUDRAGITfi RL/RS de ciertas realizaciones se pueden
20 mezclar en cualquier proporción deseada para obtener en ültimo tØrmino un
recubrimiento que enmascara ci sabor con un perfil deseable de disolueiOn del fÆnnaco.
Se pueden obtener formulaciones de liberación controlada de ciertas realizaciones, por
ejemplo, a partir de un recubrimiento retardador derivado de 100% de EUDRAGITfi RL; 50% de EUDRAGITfi RL con 50% de EUDRAGITfi RS; y 10% de EUDRAGITfi RL
W25 con 90% de EUDRAGITfi RS.

En otras realizaciones de la forma farmacØutica de matriz, el poifmero que enmascara ci
sabor puede ser un polimero acrilico de carÆctercatiOnico a base de metacrilato de dimetiiaminoetilo y Østeres del ÆcidometacrIlico neutros (EUDRAGITfi E). Los
30 recubrimientos de polfmero acrflico hidrOfobo de la presente invención pueden incluir
ademÆsun copoilmero neutro a base de poii(met)acrilatos, como EUDRAGITfi NE. Las peliculas de laca de EUDRAGITfi NE 30D son insolubles en agua y lIquidos digestivos, pero permeabies e hinchabies.

35 En otras realizaciones de la forma farmacØutica de matriz, ci polimero que enmascara el
sabor es una dispersion de poii(acrilato de etilo, metacrilato de metilo) 2:1
(KOLLICOATfi EMM 30 D).

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En otras realizaciones de la forma farmacØutica de matriz, el polImero que enmascara ci sabor puede ser un acetato polivinflico estabilizado con polivinilpirrolidona y lauril
sulfato de sodio como KOLLICOATfi SR30D.

Otros polfmeros que enmascaran el sabor y que pueden ser usados en las formas farmacØuticas de matriz incluyen hidroxipropilcelulosa (HPC);
hidroxipropilmetilcelulosa (HPMC); hidroxietilcelulosa; gelatina; gelatina/acacia; geiatina!acacialvinilmetilØter-anhfdrido maleico; gelatinalacacialanhIdrido etilenmaleico;
10 carboximetilcelulosa; alcohol polivinilico; nitrocelulosa; copoilmeros ertados de
alcohol polivinIlico-polietilenglicol; laca; cera y sus mezcias.

Los recubrimientos que enmascaran el sabor se pueden aplicar a las matrices a partir de
una o mÆssoluciones o suspensiones de disolventes orgÆnicos o acuosos. Enal menos
15 una reaiización de las formas farmacØuticas de matriz los disolventes orgÆnicos quese
pueden usar para aplicar los recubrimientos que enmascaran el sabor incluyen uno o mÆs entre acetona, alcoholes inferiores como etanol, isopropanol y mezclas de alcohoi/agua, hidrocarburos clorados y similares. Los dispositivos empleados para recubrir las matrices
de ciertas realizaciones con un recubrimiento que enmascara el sabor incluyen los
20 utilizados convencionalmente en ci procesamiento farmacØutico, como los dispositivos de
recubrimiento de lecho fluidizado. Los recubrimientos de liberación controlada aplicados
a las matrices pueden contener ingredientes diferentes de los poilmeros celuiósicos.
TambiØn se pueden usar uno o mÆs colorantes,aromatizantes y edulcorantes en el recubrimiento que enmascara ci sabor.
 25

En algunas realizaciones de las formas farmacØuticas de matriz se puede incluir un
formador de poros en ci recubrimiento que enmascara ci sabor para influir en la velocidad
de liberación del bromhidrato de bupropion desde la matriz. En otras realizaciones, no se incluye un formador de poros en ci recubrimiento que enmascara ci sabor. Los
30 formadores de poros pueden ser inorgÆnicos u orgÆnicosy pueden ser de naturaleza
particulada e incluir materiales que se pueden disolver, extraer o lixiviar del
recubrimiento en ci ambiente de uso. DespuØs de la exposición a ifquidos en ci ambiente
de uso, los formadores de poros se pueden, por ejemplo, disolver y se forman canales y
poros que se ilenan con ci lIquido ambiental.
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Por ejemplo, los formadores de poros de ciertas realizaciones de las formas farmacØuticas
de matriz pueden comprender uno o mÆs poifmeroshidrOfiios solubles en agua para

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modificar las caracteristicas de liberación de la formulación. Los ejemplos de los
poilmeros hidrOfilos adecuados que se pueden usar como formadores de poros incluyen hidroxipropilmetileelulosa, Øteres de celulosa y derivados proteicos de estos poilmeros,
los Øteres de celulosa, como hidroxialquilcelulosas, carboxialquilcelulosas y sus mezclas.
5 AdemÆs, sepueden usar poilmeros solubles en agua sintØticos, cuyos ejemplos incluyen
polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de polietileno, polidextrosa soluble en agua, sacÆridosy poIisacridos, como pullulan, dextrano, sacarosa, glucosa, fructosa, manitol, lactosa, inanosa, galactosa, sorbitol y sus mezelas. En at rnenos una realizaciOn, el poilmero hidrófilo comprende hidroxipropilmetilcelulosa.
10

Otros ejemplos no limitantes de formadores de poros que se pueden usar en el
recubrimiento que eninascara el sabor incluyen sales de metales alcalinos como
carbonato de litio, cloruro de sodio, bromuro de sodio, cloruro de potasio, sulfato de
potasio, fosfato de potasio, acetato de sodio, citrato de sodio y sus mezclas. Los sólidos
15 formadores de poros tambiØn pueden ser poilmeros solubles en el ambiente de uso, como
los CARBOWAXTM y CARBOPOLTM. Ademªs, los formadores de poros abarcan dioles, polioles, alcoholes polihidricos, polialquilenglicoles, poliglicoles, poli(a-w)alquilendioles
y sus mezclas. Otros formadores de poros que pueden ser ütiles en las formulaciones de
ciertas realizaciones de la presente invención incluyen almidón, almidón modificado y
20 derivados del almidón, gomas, incluidas, pero no exclusivamente, goma xantano, Æcido
alginico, otros alginatos, bentonita, veegum (silicato de aluminio y magnesio), agar,
goma guar, goma de algarrobo, goma arabiga, quince psyllium, semilla de lino, goma de quirnbombo, arabinogalactano, pectina, goma tragacanto, escieroglucano, dextrano,
. amilosa, amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de
25 intercambio iónico, como polimetacrilato de potasio, carragenina, carragenina kappa,
carragenina lambda, goma karaya, goma biosintØtica, y sus mezclas. Otros formadores
de poros incluyen materiales ütiles para hacer lÆminasmicroporosas en los ambientes de
uso, como policarbdnatos compuestos de poliØsteres lineales del Æcidocarbónico en los
que los grupos carbonato reaparecen en la cadena polimØrica, materiales microporosos
30 como bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas,
copolimeros modacrilicos microporosos, estireno-acrilico microporoso y sus
copolimeros, polisulfonas porosas, poli(vinilideno) balogenado, policloroØteres,
polimeros de acetal, poliØsteres preparados por esterificación de un Æcido dicarboxIlicoo anhidrido con un alquilenpoliol, poli(sulfuros de alquileno), fenOlicos, poliØsteres,
35 poilmeros porosos asimØtricos, pollmeros olefinicos reticulados, homopolimeros
hidrófilos microporosos, copolimeros o interpoilmeros con una menor densidad aparente
y otros materiales similares, poli(uretano), poli(uretano) reticulado de cadena extendida,

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poli(imidas), poli(benzimidazoles), colodión, protelnas regeneradas,
poli(vinilpirrolidona) reticulada semisólida y sus m.ezcias.

En general, la cantidad de formador de poros incluida en los recubrimientos que
5 enmascaran el sabor de ciertas realizaciones de las formas farmacØuticas de matriz puede
ser de aproximadamente 0,1% a aproximadamente 80% en peso, incluidos todos los
valores y rangos intermedios, en relación con el peso combinado de polImero y formador
de poros. Como el poreentaje de formador de poros se relaciona con ci peso seco del polimero que enmascara el sabor, puede tener una influencia en las propiedades de
10 liberación del fÆrrnaco desde la micropartIcula recubierta. En al menos una realización
que usa formadores de poros solubles en agua como hidroxipropilmetilcelulosa, puede
haber presente una relación de pesos secos de polImero que enmascara el sabor:formador
de poros de aproximadamente 10:1 a aproximadamente 1:1, incluidos todos los valores y rangos intermedios. En ciertas realizaciones la relación de pesos secos de poilmero que
15 enmascara el sabor:forrnador de poros es de aproximadamente 8:1 a aproximadamente
1,5:1, incluidos todos los valores y rangos intermedios; y en otras realizaciones de aproximadamente 6:1 a aproximadamente 2:1, incluidos todos los valores y rangos intermedios. En al menos una realización que usa EUDRAGITfi NE30D como polfmero
que enmascara el sabor y una hidroxipropilmetilcelulosa (viscosidad aprox. 5 cp (en una
20 solución acuosa a! 2%)) como METHOCELfi E5, PHARMACOATfi 606G como el
formador de poros soluble en agua, estÆ presente unarelación de pesos secos polImero
que enmascara ci sabor:fôrmador de poros de aproximadamente 2:1.

Los colorantes que se pueden usar en el recubrimiento que enmascara ci sabor de ciertas
1025 realizaciones de las formas farmacØuticas de matriz incluyen los colorantes de alimentos,
fÆrmacosy cosmØticos (FD&C), de fÆrmacosy cosmØticos (D&C), o los colorantes
externos (Ext. D&C). Estos colorantes son tinturas, laeas y ciertos colorantes naturales y derivados. Las lacas Utiles incluyen tinturas absorbidas sobre hidróxido de aluminio u
otros soportes adecuados.
30

Los saborizantes que se pueden usar en ci recubrimiento que enmascara el sabor de
ciertas realizaciones de las formas farmacØuticas de matriz incluyen lIquidos saborizantes naturales y sintØticos. Una lista ilustrativa de dichos saborizantes incluye aceites volÆtiles,aceites saborizantes sintØticos, compuestos aromÆticossaborizantes, aceites,
35 lIquidos, oleorresinas y extractos derivados de plantas, hojas, fibres, frutos, tallos y sus
combinaciones. Una lista representativa, no limitante, de Østos incluye aceites citricos,
como de limón, naranja, toronja, lima y pornelo y esencias de frutas, incluidas manzana,

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pera, durazno, uva, frutiila, frambuesa, cereza, ciruela, ananÆs, albaricoqueu otros saborizantes de fruta. Otros saborizantes iitiles incluyen aidehIdos y &steres, como benzaldehido (cereza, almendra); citral, es decir, aifa citral (lirnOn, lima); neral, es decir,
beta citral (limón, lima); decanal (naranja, limon); aldehido C-8 (citricos); aldehido C-9 (citricos); aldehido C-12 (citricos); tolil aldehido (cereza, almendra); 2,6-dimetiloctanal
(fruto verde); 2-dodenal (mandarina); y sus mezclas.

Los edulcorantes que se pueden usar en ci recubrimiento que enmascara el sabor de
ciertas realizaciones de las formas farmacØuticas de matriz incluyen giucosa (jarabe de
10 maIz), dextrosa, azücar invertido, fructosa y sus mezclas (cuando no Se usa como un
vehiculo); sacarina y sus diversas sales, como la sal de sodio; dipØptidos edulcorantes
como ci aspartamo; compuestos dihidrochalcona, glicirricina; Steva Rebaudiana (esteviosido); derivados clorados de sacarosa como sucralosa; y alcoholes de azücares
como sorbitol, mariitol, xilitol y similares. TambiØn estÆn contemplados los hidrolizados
15 de aimidOn hidrogenados y los edulcorantes sintØticos como 3,6-dihidro-6-metil-1-1-
1,2,3-oxatiazin-4-1-2,2-di6xido, en particular la sal de potasio (acesulfamo-K) y sus sales
de sodio y caicio. Los edulcorantes se pueden usar solos o en cualquier cornbinación.

El recubrimiento que enmascara ci sabor de la matriz tambiØn puede incluir uno o mÆs
20 excipientes farmacØuticamente aceptables como lubricantes, emuisionantes,
antiespumantes, plastificantes, disolventes y similares.

Se pueden incluir lubricantes para ayudar a reducir la fricción de las matrices recubiertas durante la fabricación. Los lubricantes que Se pueden usar en ci recubrimiento que
25 enmascara ci sabor de ciertas realizaciones de la presente invención incluyen, pero no
exciusivamente, Æcido adipico, estearatode magnesio, estearato de caleb, estearato de
cinc, silicato de calcio, silicato de magnesio, aceites vegetales hidrogenados, cloruro de sodio, esterotex, polioxietiieno, monoestearato de glicerilo, taico, polietilenglicol,
benzoato de sodio, lauril sulfato de sodio, lauril sulfato de magnesio, estearil fumarato de
30 sodio, aceite mineral ligero, Østeres de Æcidosgrasos como behenato de glicerilo, (por
ejemplo COMPRITOLTM), STEAR-O-WETTM, MYVATEXTM TL y sus mezclas. En al menos una realización, el lubricante se selecciona entre estearato de magnesio, talco y
una mezcia de los mismos. El lubricante puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 100% en peso del peso seco del polimero en ci
35 recubrimiento que enmascara ci sabor, inciuidos todos los valores y rangos intermedios.
Por ejemplo, en ciertas realizaciones en las que ci poilmero que enmascara ci sabor es EUDRAGITfi NE30D o EUDRAGITfi NE40D junto con un formador de poros

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hidrófilo, ci lubricante estÆpresente en una cantidad entre aproximadamente 1% y aproximadamente 30% en peso del peso seco del poilmero, incluidos todos los valores y rangos intermedios; en otras realizaciones entre aproximadamente 2% y
aproximadamente 20%, incluidos todos los valores y rangos intermedios; y aun en otras
5 realizaciones en aproximadamente 10% en peso del peso seco del recubrimiento que
emiiascara el sabor de la matriz. En otra realización en la que el polImero que enmascara
el sabor es etilcelulosa (ETHOCELTM polimero PR100, PR45, PR20, PR10 o PR7, o una mezcla), ci lubricante puede estar presente en una cantidad entre aproximadamente 10%
y aproximadamente 100% en peso del peso seco del recubrimiento que enmascara ci
10 sabor de la matriz, incluidos todos los valores y rangos intermedios; en otra reaiización

15

entre aproximadamente 20% y aproximadamente 80%, incluidos todos los valores y
rangos intermedios; y aun en otras realizaciones en aproximadamente 50% en peso del
peso seco del recubrimiento que enmascara el sabor de la matriz. En otras realizaciones,
el recubrimiento que enmascara el sabor no incluye un formador de poros.

Se pueden incluir uno o tnÆs emulsionantes(tambiØn denominados emulsionantes o emulgentes) en ci recubrimiento que enmascara el sabor de la matriz para facilitar la emulsificación real durante la fabricación del recubrimiento y tambiØn para asegurar la estabilidad de la emulsion durante la vida ütii en depósito del producto. Los
20 emulsionantes ütiles para ci recubrimiento que enmascara ci sabor de la matriz de ciertas
realizaciones incluyen, pero no exelusivamente, materiales de origen natural y sus
derivados semisintØticos, como los polisacÆridos,asI como Østeres de glicerol, Øteres de celulosa, Østeres de sorbitÆn (por ejemplo,monooleato de sorbitÆno SPANTM 80) y
polisorbatos (por ejemplo, TWEENTM 80). Las combinaciones de emulsionantes son
025 factibles. En al menos una realización, ci emulsionante es TWEENTM 80. El o los
emulsionante(s) pueden estar presentes en una cantidad entre aproximadamente 0,01% y aproximadamente 5% en peso del peso seco del poilmero que enmascara ci sabor de la
matriz, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas
realizaciones ci emulsionante estÆ presenteen una cantidad entre aproximadamente
30 0,05% y aproximadamente 3%, incluidos todos los valores y rangos intermedios; en otras
realizaciones entre aproximadamente 0,08% y aproximadamente 1,5%, incluidos todos
los valores y rangos intermedios; y aun en otras realizaciones en aproximadamente 0,1%
en peso del peso seco del poilmero que enmascara ci sabor de la matriz.

35 Se pueden incluir uno o mÆsantiespumantes en ci recubrimiento que enmascara ci sabor
de la matriz para reducir la producción de burbujas o de espuma durante la fabricación
del recubrimiento. Los antiespumantes ütiles para la composición del recubrimiento

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incluyen, pero no exciusivamente, simeticona, poliglicol, aceite de silicio y sus mezclas.
En al menos una realización, ci antiespumante es simeticona C. El antiespumante puede estar presente en una cantidad entre aproximadamente 0,1% y aproximadamente 10% del peso del recubrimiento que enmascara el sabor de la matriz, incluidos todos los valores y
5 rangos intermedios. Por ejemplo, en ciertas realizaciones el antiespumante estÆ presente
en una cantidad entre aproximadamente 0,2% y aproximadamente 5%, incluidos todos
los valores y rangos intermedios; en otras realizaciones entre aproximadamente 0,3% y aproximadamente 1%, incluidos todos los valores y rangos intermedios; y ann en otras realizaciones en aproximadamente 0,6% en peso del peso seco del poilmero que
10 enmascara ci sabor de la matriz.

Se pueden incluir uno o mÆspiastificantes en ci recubrimiento que enmascara ci sabor de
. la matriz para proporcionar mayor flexibilidad y durabilidad durante la fabrieación. Los
piastiflcantes que se pueden usar en ci recubrimiento que enmascara ci sabor de la matriz
15 de ciertas realizaciones ineluyen monogliceridos acetilados; acetil tributil citrato, butil
ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil
etil glicolato; glicerina; propiienglicoi; triacetina; tripropioina; diacetina; ftalato de
dibutilo; monoglicØrido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino;
aceite de coiza, aceite de oliva, aceite de sØsamo, citrato de trietilo; alcoholes
20 polihIdricos, glicerol, glicerina, sorbitol, Østeres de acetato, triacetato de glicerol, acetil
trietil citrato, ftalato de dibenciio, ftalato de dihexilo, octil ftalato de butilo, Mato de di isononilo, octil ftalato de butilo, azelato de dioctilo, talato epoxidado, trimelitato de
triisoctiio, ftalato de dietiihexiio, ftalato de di-n-octilo, ftalato de di-i-octilo, ftalato de di-
. i-deciio, ftalato de di-n-undeciio, ftalato de di-n-trideciio, trimelitato de tri-2-etilhexilo,
25 adipato de di-2-etilhexilo, sebacato de di-2-etilhexilo, azelato de di-2-etilhexilo, sebacato
de dibutilo, oxalato de dietilo, malato de dietilo, fumarato de dietilo, succinato de
dibutilo, malonato de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de
glicerol y sus mezcias. El piastificante puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 80% del peso seco del poilmero que
30 enmascara ci sabor, incluidos todos los valores y rangos intermedios. Por ejemplo, en
ciertas realizaciones ci piastificante estÆpresente en una cantidad entre aproximadamente
5% y aproximadamente 50%, incluidos todos los valores y rangos intermedios; en otras realizaciones entre aproximadamente 10% y aproximadamente 40%, incluidos todos los valores y rangos intermedios; y aim en otras realizaciones en aproximadamente 20% del
35 peso seco del poilmero que enmascara ci sabor.

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En algunas realizaciones, se proporcionan mezclas de plastificantes, por ejemplo, una mezcla de PEG 4000 y sebacato de dibutilo (DBS). Por ejemplo, en un comprimido de bromhidrato de bupropion de 174 mg, PEG4000 estÆ presente en una cantidad de 1,6% en peso de la formulación total y DBS estÆ presente en unacantidad de 0,8% en peso de la
5 formulaeión total, en un comprimido de bromhidrato de bupropion de 348 mg, PEG4000
estÆ presenteen una cantidad de 0,9% en peso de la formulación total y DBS cstÆ
presente en una cantidad de 0,4% en peso de la formulación total y en un comprimido de bromhidrato de bupropion de 522 mg, PEG4000 estÆ presente en una cantidad de 0,9% en peso de la formulación total y DBS estÆ presente en una cantidadde 0,4% en peso de la
10 formulación total.

El recubrimiento que enmascara el sabor puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 90% en peso de la matriz, incluidos todos los valores y rangos intermedios, dependiendo de la elección del polimero, la relación
15 polImero:formador de poros y el area superficial total de la formulaciOn de la matriz.
Puesto que tiene que lograrse un cierto espesor del recubrimiento que enmascara el sabor para lograr un enrnascaramiento eficaz del sabor, la cantidad de recubrimiento de
polimero que enmascara el sabor usada durante la fabricación estÆ relacionada con el area superficial total del lote de matrices sin recubrir que requiere un recubrimiento. Por
20 ejemplo, la cobertura del area superficial del polimero que enmascara el sabor puede
variar de aproximadamente 0,5 mg/cm2 a aproximadamente 20 mg/cm2, incluidos todos
los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones la cobertura del
area superficial del polimero que eninascara el sabor es de aproximadamente 0,6 mg/cm2
a aproximadamente 10 mg/cm2, incluidos todos los valores y rangos intermedios, y en
025 otras realizaciones es de aproximadamente 1 mg/cm2 a aproximadamente 5 mg/cm2,
incluidos todos los valores y rangos intermedios. En al menos una realización de la
invención, se emplea EUDRAGITfi B como el polimero que enmascara el sabor a una
cobertura de area superficial de 4 mg/cm2.

30 A falta de una determinación exacta del area superficial total de una matriz, la cantidad
de polimero que enmascara el sabor que se debe aplicar se puede expresar como un
poreentaje de la matriz sin recubrir. Por ejemplo, en ciertas realizaciones el
recubrimiento que enmascara el sabor estª presente en una cantidad entre
aproximadamente 5% y aproximadamente 60%, incluidos todos los valores y rangos
35 intermedios; en otras realizaciones entre aproximadamente 10% y aproximadamente
40%, incluidos todos los valores y rangos intermedios; y aun en otras realizaciones entre aproximadamente 15% y aproximadamente 35% en peso de la matriz, incluidos todos los

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valores y rangos intermedios. En a! menos una realización, el recubrimiento que
enniascara el sabor estÆpresente en una cantidad de aproximadamente 30% en peso de la matriz.

5 Los ejemplos profØticos de las formulaciones de comprimidos de matriz se describen a
continuación. Se debe comprender que estos ejemplos estSn destinados a ser ejemplares
y que los constituyentes especIficos, sus cantidades y mØtodos de formulación se pueden variar para lograr diferentes caracteristicas de liberación:

10 En al menos una realizaeión, las matrices controladas comprenden:
Bupropion HBr aproximadamente 30,0% en peso de la
matriz

Hidroxipropilmetilcelulosa E50 aproximadamente 10,0% en peso de la matriz
Hidroxipropilmetilcelulosa K 5M aproximadamente 30,0% en peso de la matriz
15 Fosfato de calcio deshidratado aproximadamente 9,5% en peso de la matriz
ATMULTM 84S aproximadamente 20,0% en peso de la matriz
(mono/di/tri gliceridos)
Estearato de magnesio aproximadamente 0,5% en peso de la matriz

20 La preparación de la formulación de la matriz puede set la siguiente: Combinar el
fÆrmaco,una porciOn de HPMC, de fosfato de calcio y de Atmul 84S en un mezclador planetario y mezclar en seco durante 15 minutos. Agregar una solución del resto de la HPMC en agua al mezclador mientras se mezcla, hasta que se obtenga una masa hümeda. Pasar el material hümedo a travØs de un tamiz para hacer los grÆnulosresultantes de
25 tamaflo uniforme (para lograr un secado uniforme) y secar en una estufa a
aproximadamente 40°C durante aproximadamente 24 horas. Moler los grÆnulos secos a travØs de un molino Fitzpatrick, con cuebillas delanteras, y recoger el material en un mezclador. Agregar ci estearato de magnesio y mezciar durante aproximadamente 5 minutos. La mezela resultante se comprime en una compresora de comprimidos
30 adecuada.

En al menos una realización, las matrices de liberación controlada comprenden un ntc1eo
de depósito y una plataforma de soporte. La preparación del nücleo de depósito puede
5cr la siguiente: Los nücleos de depósito se pueden preparar usando los materiales
35 siguientes en las cantidades establecidas:
Bupropion HBr aproximadamente
45,Og

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Hidroxipropilinetilcelulosa (METHOCELfi K 100 M-Colorcon) aproximadamente
35,0 g
manitol

etilcelulosa (alta viscosidad-BD1)
3,75 g estearato de magnesio
mezcla 5:1 de etanol-cloroformo

aproximadamente 10,0 g
aproximadamente 3,75g
aproximadamente 1,0 g
aproximadamente 75,0 ml

El bromhidrato de bupropion se mezcla bien con el manitol y la hidroxipropilmetilcelulosa en un mezclador adecuado. La solución de etilcelulosa en etanol-cloroformo se prepara por separado y se usa para humedecer la mezcla de polvos obtenida previamente. La masa homogØnea resultante se fuerza a travØs de un tamiz de 800 micras y luego se seca para obtener un granulado que se pasa a travØs de un tamiz de 420 micras. El granulado homogØneo obtenido se mezela con ci estearato de magnesio y luego se comprime usando punzones cOncavos de 7 mm de diametro (radio de curvatura de 9 mm) usando una presión de aproximadamente 3.000 kg/cm2 para obtener nücieos de depOsito cilIndricos con bases convexas.

La aplicación de la plataforma de soporte puede 5cr del modo siguiente: La plataforma de soporte se puede aplicar recubriendo una o ambas bases convexas del nücleo de depósito con una solución de aproximadamente 15 g de copolimero acrIlico-metacrIlico de baja permeabilidad (EUDRAGITfi RS) en cloruro de metileno en una cantidad para obtener 100 ml. Posteriormente se aplican aproximadamente 0,3 ml de dieha solución a cada base que se va a recubrir, teniendo cuidado de proteger la superficie lateral del niicieo. DespuØs ci sistema se seca con aire tibio. La cantidad de material polimØrico depositado es suficiente para mantener la estructura intacta durante la transferencia.

En al menos una realización, la formulación de la matriz es una formulación de matriz de comprimido basada en óxido de polietileno (OPE) que comprende:
Bromhidrato de bupropion aproximadamente 50%
OPE WSR Coagulante
(óxido de polietileno)
METHOCELfi K100M
(hidroxipropilmetilcelulosa)
Avicel PH101
(celulosa microcristalina)
Estearato de magnesio

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aproximadamente 15%

aproximadamente 15%

aproximadamente 19%

aproximadamente 1%

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La preparación de la formulación de matriz de comprimido basada en OPE puede
ser la siguiente: Los excipientes se mezelan en seco en un mezclador apropiado y se comprimen en forma de comprimidos usando equipos convencionales.

5 Multiparticulados
En ciertas realizaciones de la presente invenciOn, se proporciona un sistema
multiparticulado que contiene micropartIculas miltiples que cada una contiene una
cantidad eficaz de bromhidrato de bupropion y al menos un excipiente
farmacØuticamente aceptable. Los multiparticulados pueden estar contenidos dentro de
10 una cÆpsula,o se pueden comprimir en forma de matriz o comprimido, que al ingerir se
disuelven en multiples unidades (por ejemplo, pelets), donde las subunidades o pelets poseen las propiedades deseadas de liberación controlada de la forma farmacØutica. Los multiparticulados o las formas farmacØuticas muiltiples pueden estar rodeados por uno o mÆsrecubrimientos. Los ejemplos de dichos recubrimientos incluyen recubrimientos
15 polimØrieos de liberación controlada, recubrimientos de liberación retardada,
recubrimientos entØricos, recubrimientos de liberación inmediata, recubrimientos que enmascaran el sabor, recubrimientos de liberación extendida y recubrimientos no
funcionales.

20 La sal bromhidrato de bupropion en las micropartIculas de ciertas realizaciones puede
estar presente en una cantidad eficaz entre aproximadamente 0,1% y aproximadamente
99% en peso de las micropartfculas, incluidos todos los valores y rangos intermedios.
Por ejemplo, en ciertas realizaciones el bromhidrato de bupropion estÆ presenteen las
. micropartIculas en una cantidad entre aproximadamente 0,1% y aproximadamente 90%,
25 incluidos todos los valores y rangos intermedios, en otras realizaciones entre
aproximadamente 5% y aproximadamente 90%, incluidos todos los valores y rangos intermedios, aun en otras realizaciones entre aproximadamente 10% y aproximadamente
80%, incluidos todos los valores y rangos intermedios, y todavIa en otras realizaciones
entre aproximadamente 25% y aproximadamente 80% en peso de la micropartleula,
30 incluidos todos los valores y rangos intermedios. En ciertas realizaciones en que las
micropartfculas se preparan usando un proceso de esferonización, el bromhidrato de bupropion puede estar presente en las micropartIculas en una cantidad entre aproximadamente 0,1% y aproximadamente 60%, incluidos todos los valores y rangos intermedios; en otras de dichas realizaciones entre aproximadamente 5% y
35 aproximadamente 50%, incluidos todos los valores y rangos intermedios; y aün en otras
de dichas realizaciones entre aproximadamente 10% y aproximadamente 40% en peso de
la micropartIcula, incluidos todos los valores y rangos intermedios. En al menos una

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realizacion en donde las microparticulas se preparan usando un proceso de esferonizacion (
el bromhidrato de bupropion estÆpresente en la micropartIcula en una cantidad de aproximadamente 30% en peso de la micropartIcula.

5 AdemÆsde la sal bromhidrato de bupropion, las microparticulas de la presente invención
tambiØn incluyen al menos tin excipiente farmacØuticamente aceptable. Se pueden
agregar excipientes para facilitar la preparación, la aceptabilidad por el paciente y la
acción de la forma farmacØutica como un sistema de liberación del fÆrmaco. Los
ejemplos de posibles excipientes incluyen auxiliares de esferonizaciOn, potenciadores de
10 la solubilidad, desintegrantes, diluyentes, lubricantes, aglutinantes, rellenos, deslizantes,
agentes de suspension, emulsionantes, antiespumantes, saborizantes, colorantes, estabilizadores quimicos, modificadores del pH y sus mezclas. Dependiendo de la
función principal concebida, los excipientes que se van a usar en la formulación de composiciones se subclasifican en grupos diferentes. Sin embargo, tin excipiente puede
15 afectar a las propiedades de una composiciOn de una serie de maneras, y muchos
excipientes usados en las composiciones pueden describirse por lo tanto como multifuncionales.

Las microparticulas de ciertas realizaciones de la presente invenciOn se pueden fabricar
20 usando las tØcnicas corrientes conocidas por un tØcnico con experiencia. En ciertas
realizaciones, las microparticulas se pueden realizar de acuerdo con cualquiera de los
mØtodos descritos en el presente. Las microparticulas ütiles incluyen micropartfculas distribuidas en capas de fÆrmacoy microparticulas que contienen fÆrrnaco.

 5 Microparticulas que contienen fÆrmaco
Las microparticulas que contienen fÆnnacoen el nücleo se pueden preparar mediante una
serie de procedimientos diferentes. Por ejemplo: En un proceso de secado por aspersion,
se pulveriza una soluciOn acuosa de material del nücleo y una solución caliente de
poilmero en el aire caliente, despuØs se evapora el agua y el sOlido seco se separa en
30 forma de pelets, por ejemplo por suspension en aire. Un proceso de secado por aspersion
puede producir pelets huecos cuando el lIquido se evapora a una velocidad que es mayor
que la de la difusiOn de las sustancias disueltas de vuelta en el interior de la gotita, 0 51 se debe a la acción capilar la sustancia disuelta migra hacia afuera con el lIquido a la
superficie de la gotita, dejando detrªs un vaclo. Otro ejemplo es an proceso de
35 congelaciOn por pulverizaciOn, donde una suspension acuosa espesa del material
farmacolOgico que es insoluble en una masa fundida se congela por pulverización para obtener partIculas discretas de los materiales insolubles recubiertos con la sustancia

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congelada. Otro ejemplo es un proceso de granulacionlpeletizacion basado en un lecho fluidizado, donde un frmaco seco se suspende en una corriente de aire caliente para
formar un lecho fluidizado constantemente agitado. Una cantidad de lIquido aglutinante
o de granulaciOn se introduce luego en forma finamente dispersa para causar peletización.

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Las microparticulas que contienen fÆrmaco de ciertasrealizaciones de la presente
invención tambiØn se pueden hacer mediante, por ejemplo, un proceso de esferonización.
Un mØtodo de fabricación de microparticulas que contienen fÆrmaco es latecnologIa
patentada por el solicitante CEFORMTM (Microsferas/MicropartIculas Centrifugamente
10 Extruidas y Fonnadas), que consiste en el uso simultÆneode calor instantÆneoy fuerza
centriftiga, usando equipo de diseflo patentado, para convertir sistemas de polvo seco en microparticulas de tamaflo y forma unifonnes. La producciOn de micropartIculas que
. contienen un fÆrmaco activo usando latecnologIa CEFORMTM es conocida. Ciertas
realizaciones de la presente invención tratan el uso del proceso LIQUIFLASHfi para
15 esferonizar composiciones que contienen uno o mÆs fÆrmacosactivos para formar
microparticulas LIQUIFLASHfi.

Con la tecnologIa CEFORMTM, el procesamiento de las microparticulas que contienen fÆrmacode ciertas realizaciones de la presente invención se lieva a cabo de manera
20 continua, para lo cual una premezcla del fÆrmacoy los excipientes se introduce en un
"cabezal de microsfera" rotatorio, tambiØn denominada "cabezal de esferonizaciOn". El
cabezal de microsfera, que es una unidad de producción multiabertura, gira sobre sus ejes
y se calienta mediante energfa elØctrica. La premezcla de fÆrmacoy excipiente(s) se
. introduce en el centro del cabezal con un alimentador automatizado. El material se
25 mueve, mediante fuerza centrIfuga, al borde exterior donde los calentadores, ubicados en
ci borde del cabezal, calientan el material. Las microparticulas Se forman cuando el
material fundido sale del cabezal, y luego son enfriadas por convección a medida que
caen al fondo de la cmara de microparticulas. DespuØs el producto se recoge y se
almacena en los envases del producto adecuados. La selección cuidadosa de los tipos y
30 los niveles del o de los excipientes controla las propiedades de las microparticulas como
esfericidad, morfologia superficial y velocidad de disolución. Una ventaja de dicho
proceso es que las microparticulas se producen y se recogen de una carga de alimentación seca sin usar ningün disolvente.

35 Hay al menos dos mØtodos que se pueden usar para producir microparticulas que
contienen fªrmaco usando el proceso de CEFORM: (i) el mØtodo de encapsulación y (ii)
el mØtodo de co-fusion. En el mØtodo de encapsulaciOn, ci proceso se lleva a cabo por

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1) debajo del punto de fusion del fÆrmaco. Porconsiguiente, los excipientes se disefian para
fundir y arrastrar las partleulas de fªrmaco at pasar a travØs de las aberturas para formar
micropartIculas. Las mieropartleulas resuitantes contienen ci fÆrmaco,en su estado
natural, esencialmente envuelto por o corno una matriz Intima con los excipientes
5 resolidificados. En ci mØtodo de co-fusiOn, ci proceso se ileva a cabo por encima del
punto de fusion del fÆrmaco. Eneste caso, ci fÆrmacoy los excipientes se funden o se
convierten en lIquido simultÆneamenteat exponerse at calor. La mezcla fundida sale del cabezal y forma micropartIculas, que se enfrian a medida que caen at fondo de la cuba de depósito donde se recogen.
10

En at menos una realización las micropartIculas Se preparan usando ci mØtodo de encapsuiación. En ci mØtodo de encapsulación el o los excipientes que se eligen tienen
un punto de fusiOn inferior at del fÆnnaco (por ejemplo, bromhidrato de bupropion)con
ci que se combinarÆn. Por consiguienteel proceso de esferonizaciOn se puede realizar a
15 temperaturas inferiores, que el punto de fusion del fÆrmaco. Como resultado, estopuede
reducir el riesgo de interconversion polimØrica, que puede ocurrir cuando se usan temperaturas de procesamiento próxirnas at punto de fusion.

En un ejemplo profØtico de ciertas realizaciones de la presente invención, ci proceso de
20 fabricación de las micropartIcuias puede ser hipotØticamente ci siguiente: Se tamiza ci
auxiliar de esferonización a travØs de un tamiz de 425 micras (tm). En at menos una
realización, ci auxiliar de esferonizaciOn es monoestearato de glicerilo destilado (es decir DMG-03VF). Se agrega aproximadamente 50% del auxiliar de esferonización a un bol
de un mezclador de alto cizallamiento. En at menos una reaiizaciOn, ci bol es un bol de 6
025 litros y ci mezclador de alto cizallamiento es un granulador mezclador de alta velocidad
Diosna P 1-6. DespuØs se agrega ci fÆrmaco aetivo atbol del mezclador, y despuØs se
agrega ci resto del auxiliar de esferonización. DespuØs se mezcia ci material en ci
mezclador durante un tiempo entre aproximadamente 1 minuto y aproximadamente 30
minutos, incluidos todos los valores y rangos intermedios; en ciertas realizaciones, entre
30 aproximadamente 3 minutos y aproximadamente 10 minutos; y en at menos en una
realización, durante aproximadamente 6 minutos. La velocidad del motor del mezclador
es de aproximadamente 50 rpm a aproximadamente 2.000 rpm, incluidos todos los
valores y rangos intermedios; en ciertas realizaciones, de aproximadamente 200 rpm a aproximadamente 500 rpm; y en at menos una realización, aproximadamente 300 rpm.
35 La velocidad del motor de la cortadora es de aproximadamente 50 rpm a
aproximadamente 2.000 rpm, incluidos todos los valores y rangos intermedios; en ciertas realizaciones, de aproximadamente 200 rpm a aproximadamente 500 rpm; y en at menos

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una realización, aproximadamente 400 rpm. El material mezclado se esferoniza a continuaciOn en un cabezal de esferonizaciOn CEFORMTM. La velocidad del cabezal de esferonización es de aproximadamente 5 Hz a aproximadamente 60 Hz, incluidos todos
los valores y rangos intermedios; en ciertas realizaciones, de aproximadamente 10 Hz a
5 aproximadamente 30 Hz; y en al menos una realización, aproximadamente 15 Hz. En al
menos una realización el cabezal de esferonizaciOn CEFORMTM es un cabezal de 5
pulgadas. La temperatura del cabezal de esferonización se mantiene de aproximadamente
70°C a aproximadamente 130T, incluidos todos los valores y rangos intermedios; en
ciertas realizaciones de aproximadamente 90°C a aproximadamente 110°C; y en al menos
10 una realización, aproximadamente 100°C. Las microparticulas obtenidas a partir del
proceso rotatorio se tamizan despuØs a travØs de un tamiz que es de aproximadamente
150.tm a aproximadamente 800.im, incluidos todos los valores y rangos intermedios.

qw Las microparticulas elaboradas usando un proceso de esferonizaciOn como el proceso
15 CEFORMTM, incluyen, ademÆs dela sal bromhidrato de bupropion, al menos un auxiliar
de esferonización. Los auxiliares de esferonización pueden ayudar a la mezcla que
contiene fªrmaco a formar partIculas esfØricas resistentes, duraderas. Algunos ejemplos
de los materiales (itiles como auxiliares de esferonización incluyen, pero no
exciusivamerite, monoestearato de glicerilo, behenato de glicerilo, dibehenato de
20 glicerilo, palmitoestearato de glicerilo, aceites hidrogenados como el aceite de ricino
hidrogenado comercializado con el nombre CUTINATM HR, sales de Æcidos grasoscomo estearato de magnesio o estearato de calcio, polioles como manitol, sorbitol, xilitol, Æcido esteÆrico, Æcido palmitico,lauril sulfato de sodio, Øteres polioxietilØnicos, polioxietilenos esterificados como distearato de PEG-32, distearato de PEG-150, alcohol cetoestearilico,
25 ceras (por ej emplo, cera camauba, cera blanca, cera de parafina) y materiales semej antes
a cera. Ciertos polImeros termoplÆsticoso ablandados por calor tambiØn pueden aetuar
como auxiliares de esferonización. Algunos ejemplos no limitantes de dichos polimeros termoplÆsticoso ablandados por el calor incluyen povidona, Øteres de celulosa y
alcoholes polivinilicos. Se pueden usar combinaciones de auxiliares de esferonización.
30 En al menos una realización, el auxiliar de esferonizaciOn es monoestearato de glicerilo
(es decir DMG-03VF). El auxiliar de esferonización puede estar presente en una
cantidad entre aproximadamente 0,1% y aproximadamente 99% en peso del peso de la micropartfcula, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el auxiliar de esferonizaciOn estÆpresente en una cantidad entre
35 aproximadamente 5% y aproximadamente 90%, incluidos todos los valores y rangos
intermedios, en otras realizaciones entre aproximadamente 10% y aproximadamente
80%, incluidos todos los valores y rangos intermedios, aun en otras realizaciones entre

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aproximadamente 20% y aproximadamente 70%, incluidos todos los valores y rangos intermedios, y todavIa en otras realizaciones entre aproximadamente 30% y aproximadamente 60% en peso de la micropartIcula, incluidos todos los valores y rangos intermedios. En al menos una realización el auxiliar de esferonización estÆ presente en
una cantidad de aproximadamente 50% en peso de la micropartIcula. En al menos otra realización, las micropartIculas incluyen aproximadamente 50% (pIp) de bromhidrato de bupropion y aproximadamente 50% (pIp) del auxiliar de esferonización.

En ciertas realizaciones, cada micropartIcula tambiØn puede incluir al menos un
10 potenciador de la solubilidad. Los potenciadores de la solubilidad pueden ser agentes
tensioactivos. Ciertas realizaciones de la invención incluyen un potenciador de la solubilidad que es un tensioactivo hidrófilo. Los tensioactivos hidrófiios se pueden usar para proporcionar a las composiciones cualquiera de varias caracterIsticas ventajosas, incluidas: mayor solubilidad de la sal bromhidrato de bupropion en la micropartIcula;
15 mejor disolución de la sal bromhidrato de bupropion; mejor solubilización de la sal
bromhidrato de bupropion al disolverse; mejor absorción y/o biodisponibilidad de la sat bromhidrato de bupropion. El tensioactivo hidrófilo puede ser un ünico tensioactivo
hidrófilo o una mezcla de tensioactivos hidrófilos y puede ser iónico o no iónico.

20 Asimismo, otras varias realizaciones de la invención incluyen un componente lipófilo,
que puede ser un tensioactivo lipófilo, incluida una mezcla de tensioactivos lipófilos, un triglicØrido o una mezcla de Østos. El tensioactivo lipófilo puede proporcionar cualquiera
de las caracterJsticas ventajosas mencionadas antes para los tensioactivos hidrófilos, asI
como mejorar aün mÆs la función de los tensioactivos. Estas diversas realizaciones Sc describen en mÆsdetalie a continuaciOn.

Como es bien conocido en ci area, los tØrminos ’hidrófilos" y "lipófilos" son tØrminos relativos. Para actuar como un tensioactivo, un compuesto incluye porciones polares o hidrófilas cargadas asi como porciones apolares hidrófobas (lipofilas); es decir, un
30 compuesto tensioactivo es anfifihico. Un parÆmetroempIrico comi.nmente utilizado para
caracterizar la hidrofilicidad y lipofihicidad relativas de los compuestos anfifihicos no
iónicos es ci equilibrio hidrófilo-lipofihico (el valor "EHL"). Los tensioactivos con
valores de EHL bajos son mÆslipófilos y tienen mayor solubilidad en los aceites,
mientras que los tensioactivos con valores de EHL mayores son mÆs hidrófilos y tienen
35 mayor solubilidad en las soluciones acuosas.

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Usando los valores de EHL como una gula aproximada, se puede considerar que los tensioactivos hidrOfilos son en general los compuestos que tienen un valor de EHL
superior a aproximadamente 10, asI como los compuestos aniónicos, catiónicos o zwiteriónicos Para los cuales no es aplicable la escala de EHL. De la misma manera, los
5 tensioactivos lipófilos pueden ser los compuestos que tienen un valor de EHL menor de
aproximadamente 10.

Se debe apreciar que ci valor de EHL de un tensioactivo es solo una guIa aproximada que
se usa generalmente Para permitir la formulación de emuisiones industriales,
10 farmacØuticas y cosmØticas. Para muchos tensioactivos, incluidos varios tensioactivos
polietoxilados, se ha informado que los valores de EHL pueden diferir hasta en aproximadamente 8 unidades de EHL, dependiendo del mØtodo empirico elegido Para Sdeterminar ci valor de EHL (Schott, J. Pharm. Sciences, 79(1), 87-88 (1990)). Asimismo, Para ciertos copolimeros en bloque que contienen Oxido de polipropileno (poioxÆmeros,
15 que se comercializan como tensioactivos PLURONIC(t), los valores de EHL pueden no
reflejar con exactitud la naturaleza fisicoqulmica verdadera de los compuestos.
Finalmente, los productos tensioactivos comerciales generalmente no son compuestos
puros, sino que a menudo son mezclas complejas de compuestos y ci valor de EHL
informado Para un compuesto en particular puede ser mÆs exactamente caracterIstico del
20 producto comercial del cual ci compuesto es un componente principaL Diferentes
produetos comerciales que tienen ci mismo componente tensioactivo principal pueden, y generalmente es asI, tener diferentes valores de EHL. Ademªs, se espera una cierta
cantidad de variabilidad de lote-a-lote incluso Para un i’jnico producto tensioactivo
. comercial. Teniendo estas dificultades inherentes en mente y usando los valores de EHL
25 como una gufa, un tØcnico con experiencia puede identificar fÆcilmente los tensioactivos
que tienen la hidrofihicidad o lipofihicidad adecuadas Para usar en la presente invención,
segn se describe aquL

Los potenciadores de la solubilidad pueden ser cualquier tensioactivo adecuado Para usar
30 en las composiciones farmacØuticas tal como se conoce en ci area. Los tensioactivos
adecuados pueden ser aniOnicos, catiónicos, zwiteriOnicos o no iónieos. Los tensioactivos refinados, destilados o fraccionados, sus fracciones purificadas o reesterificadas, estÆn tambiØn dentro del alcance de la inyencjOn.

35 Aunque el polietilenglicol (PEG) en si no funciona como un tensioactivo, hay diversos
Østeres de ªcidos grasos con PEG adecuados que tienen propiedades tensioactivas ütiles,
tal como se conoce en ci area. Los diØsteres de Æcidosgrasos de polietilenglicol (PEG)

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tambiØn son adecuados para usar como tensioactivos en las composiciones de la presente invención, segün se conoce en el area. En general, las mezclas de tensioactivos tambiØn
son ütiles para la presente invención, incluidas mezclas de dos o mÆs productos tensioactivos comerciales tal como se conoce en el area (por ejemplo, Østeres de Æcidos
5 grasos de PEG se comercializan como mezclas de mono y di Østeres).

Se puede preparar un gran ni’imero de tensioactivos adecuados de diferentes grados de lipofflicidad o hidrofihicidad mediante la reacción de alcoholes o polioles con una diversidad de aceites naturales y/o hidrogenados, tal como se conoce en ci area. En
10 ciertas realizaciones, los aceites usados son aceite de ricino o aceite de ricino
hidrogenado o un aceite vegetal comestible como aceite de rnaiz, aceite de oliva, aceite
de manI, aceite de almendra de Palma, el aceite de grano de albaricoque o aceite de aimendra. Los ejemplos no limitantes de aicoholes incluyen glicerol, propilenglicol, etilenglicol, polietilenglicol, sorbitol, pentaeritritol y sus mezclas.

15

Los Østeres de Æcidosgrasos de poliglicerol, tal como se conocen en el area, tambiØn son tensioactivos adecuados para la presente invención. Los Østeres de ªcidos grasos de propilenglicol, tal corno se conocen en el area, tambiØn son tensioactivos adecuados para usar en la presente invención. En general, las mezclas de tensioactivos tambiØn son
20 adecuadas para usar en 14 presente invención. En particular, las mezclas de Østeres de
Æcidosgrasos de propilenglicol y Østeres de Æcidos grasosde glicerol, tal como se
conocen en el area, son adecuadas y estÆndisponibles comercialmente. Otra clase de tensioactivos adecuados es la clase de los mono y diglicØridos, tal como se conocen en ci
Area. Estos tensioactivos generalmente son lipófilos. Los esteroles y los derivados de los
 25 esteroles son tambiØn tensioactivos adecuados para usar en la presente invención, tal
como se conocen en el area. Estos tensioactivos pueden ser hidróflios o lipófilos. Se
dispone de una diversidad de Østeres de ªcidos grasos de PEG-sorbitÆn conocidos en el
area que se encuentran disponibles y son adecuados para usar como tensioactivos en la
presente invención. En general, estos tensioactivos son hidrófilos, aunque se pueden usar
30 varios tensioactivos lipófiios de esta clase. Los Øteres de polietilenglicol y
alquilalcoholes adecuados son conocidos en el area y son tensioactivos apropiados para
usar en la presente invención. Los Østeres de azücares son conocidos en el area y son tensioactivos adecuados para usar en la presente invención. Se dispone de varios tensioactivos hidrófilos PEG-aiquilfenol que son conocidos en el area y son adecuados
35 para usar en la presente invención.

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Los copoilmeros en bloque de OPE-OPP son una clase tinica de tensioactivos
polimØricos. La estructura ünica de los tensioactivos, con porciones OPE hidrófilas y
OPP lipófilas en relaciones y posiciones bien definidas, proporciona una amplia gama de tensioactivos adecuados Para usar en la presente invención. Estos tensioactivos se
5 comercializan con diversos nombres comerciales, incluidos la serie SYNPERONICTM PE
(ICI); la serie PLURONICfi, EMKALYXTM, LUTROLTM, SUPRONICTM,
MONOLANTM, PLURACARETM y PLURODACTM. El tØrmino genØrico Para estos
polfmeros es "poloxamero" (CAS 9003-11-6). Estos polimeros tienen la formula: HO(C2H40)a(C3H60)b(C2H40)aH
10 donde "a" y "b" indican el nümero de unidades de polioxietileno y de polioxipropileno,
respectivamente. Los tensioactivos adecuados de esta clase son conocidos en el area.

. Los Østeres de Æcidosgrasos de sorbitÆn son tensioactivos adecuadosPara usar en la
presente invención y son conocidos en el area. Los Østeres de alcoholes inferiores (C2 a
15 C4) y Æcidosgrasos (C8 a C18) son tensioactivos adecuados Para usar en la presente
invención y son conocidos en el area. Los tensioactivos iónicos, incluidos los
tensioactivos catiOnicos, aniónicos y zwiteriOnicos, son tensioactivos hidrófilos
adecuados Para usar en la presente invención y son conocidos en el area. En ciertas realizaciones, el tensioactivo es un tensioactivo aniónico como una sal de un Æcido graso,
20 una sal biliar o una combinación de Østas. En otras realizaciones el tensioactivo es un
tensioactivo catiónico como una carnitina. Los ej emplos de tensioactivos iOnicos
incluyen oleato de sodio, lauril sulfato de sodio, lauril sarcosinato de sodio, dioctil sulfosuccinato de sodio, colato de sodio, taurocolato de sodio; lauroil carnitina; palmitoil
10 carnitina; y miristoil carnitina.
25

Los tensioactivos ionizables, cuando estÆnpresentes en su forma no ionizada (neutra, no
salina), son tensioactivos lipófilos adecuados Para usar en las composiciones de la
presente invención y son conocidos en el area. Ejemplos particulares de dichos
tensioactivos incluyen Æcidos grasoslibres, en particular Æcidosgrasos C6-C22, y Æcidos
30 biliares. MÆsespecfficamente, los tensioactivos ionizables sin ionizar adecuados
incluyen las formas Æcidograso libre y Æcido biliarde cualquiera de las sales del Æcido
graso y las sales biliares.

Los derivados de las vitaminas liposolubles, como las vitaminas A, D, E, K, etc., tambiØn
35 son tensioactivos ütiles Para las composiciones de la presente invenciOn. Un ejemplo de
dichos derivados es tocoferil PEG-1.000 succinato (TPGS).

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En ciertas realizaciones, se usan tensioactivos o mezelas de tensioactivos que solidifican a temperatura ambiente. En otras realizaciones, se usan tensioactivos o mezelas de tensioactivos que solidifican a temperatura ambiente en combinación con componentes lipófilos particulares, como triglicØridos, o con adición de aditivos apropiados, como modifleadores de la viscosidad, aglutinantes, espesantes y similares.

Los ejemplos de tensioactivos hidrófilos no iónicos incluyen alquilglucOsidos; alquilmaltósidos; alquiltioglucósidos; lauril macrogolglicØridos; Øteres polioxietilen aiqullicos; polioxietilen aiquilfenoles; Østeres de Æcidosgrasos de polietilenglicol; Østeres
10 de Æcidosgrasos de polietilenglicol glicerol; Østeres de Æcidos grasos de polioxietilen
sorbitÆn;copolimeros en bloque de polioxietileno-polioxipropileno; ºsteres de Æcidos
grasos de poliglicerol; polioxietilen glicØridos; polioxietilen esteroles, sus derivados y sus anÆlogos;aceites vegetales polioxietilenados; aceites vegetales hidrogenados polioxietilenados; mezclas de reacción de polioles con Æcidosgrasos, glicØridos, aceites
15 vegetales, aceites vegetales hidrogenados y esteroles; Østeres de azüeares, Øteres de
azüeares; sucrogliceridos; vitaminas solubles en grasas polietoxiladas o sus derivados; y
sus mezclas.

En ciertas realizaciones, ci tensioactivo hidrófilo no iónico se selecciona del grupo
20 comprendido por Øteres polioxietilen aiqullicos; Østeres de Æcidos grasosde
polietilenglicol; Østeres de Æcidosgrasos de polietilenglicol y glicerol; Østeres de Æcidos grasos de polioxietilen sorbitÆn;copoilmeros en bloque de polioxietileno-
polioxipropileno; Østeres de Æcidosgrasos de poliglicerilo; polioxietilen glicØridos;
aceites vegetales polioxietilenados; aceites vegetales hidrogenados polioxietilenados y
sus mezclas. El glicerido puede ser un nionoglicerido, diglicØrido, triglicØrido o una
mezcla de Østos.

En ciertas otras realizaciones, los tensioactivos usados son tensioactivos hidrófilos no
iónicos que son mezelas de reacción de polioles y Æcidosgrasos, glicØridos, aceites
30 vegetales, aceites vegetales hidrogenados o esteroles. Estas mezelas de reacción estÆn
compuestas en gran parte de los productos de transesterificación de la reacciOn, junto con mezclas a menudo complejas de otros productos de reacción. El poliol puede ser glicerol, etilenglicol, polietilenglicol, sorbitol, propilenglicol, pentaeritritol, un sacÆrido o una
mezcla de Østos.

El tensioactivo hidrófilo tambiØn puede ser, o incluir como un componente, un
tensioactivo iOnico. Los ejeniplos de tensioactivos iónicos incluyeu sales de
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alquilamonio; sales y Æeidosbiliares, sus anÆlogosy sus derivados; ÆcidofusIdico y sus derivados; derivados Æcidosgrasos de aminoÆeidos, oligopØptidosy polipØptidos;
derivados glicØridos de aminoÆcidos, oligopØptidosy polipØptidos; lactilatos de acilo;
Østeres de Æcido tartÆrico monoy diacetilados de mono y digliceridos; morioglicØridos
5 succinilados; Østeres de Æcido citricode mono y diglicØridos; sales de alginato; alginato
de propilenglicol; lecitinas y lecitinas hidrogenadas; lisolecitina y lisolecitinas
hidrogenadas; lisofosfolipidos y sus derivados; fosfolipidos y sus derivados; sales de aiquilsulfatos; sales de Æcidos grasos; docusato desodio; carnitinas; y mezclas de Østos.

10 En ciertas realizaciones los tensioactivos iónicos incluyen sales y ªcidos biliares, sus
anÆlogosy sus derivados; lecitinas, lisolecitinas, fosfolipidos, lisofosfolIpidos y sus
derivados; sales de aiquilsulfatos; sales de Æcidosgrasos; docusato de sodiO; lactilatos de Sacilo; Østeres de Æcido tartricomono y diacetilados de mono y diglicØridos; monogliceridos succinilados; Østeres de Æcidocitrico de mono, diglicØridos; carnitinas; y
15 sus mezelas.

Los ejemplos de tensioactivos ionicos incluyen lecitina, lisolecitina, fosfatidilcolina, fosfatidiletanolamina, fosfatidilglicerol, ªcido fosfatidico, fosfatidilserina,
lisofosfatidjicolina, lisofosfatidiletanolamina, lisofosfatidilglicerol, Æcidolisofosfatidico,
20 lisofosfatidilserina, PEG-fosfatidiletanolamina, PVP-fosfatidiletanolamina, Østeres
lactIlicos de Æcidos grasos,estearoil-2-lactilato, estearoil lactilato, monoglicØridos succinilados, Østeres de ÆcidotartÆricomono/diacetilados de mono/diglicØridos, Østeres
de Æcidocitrico de mono/diglicØridos, colato, taurocolato, glicocolato, desoxicolato, taurodesoxicolato, quenodesoxicolato, glicodesoxicolato, glicoquenodesoxicolato,
25 tauroquenodesoxicolato, ursodesoxicolato, tauroursodesoxicolato, glicoursodesoxicolato,
colilsarcosina, N-metil taurocolato, caproato, caprilato, caprato, laurato, miristato,
palmitato, oleato, ricinoleato, linoleato, linolenato, estearato, lauril sulfato, teracecil
sulfato, docusato, lauroil carnitinas, palmitoil carnitinas, miristoil carnitinas y sus sales y
mezclas.
30

En ciertas realizaciones, los tensioactivos iónicos usados incluyen lecitina, lisolecitina, fosfatidilcolina, fosfatidiletanolamina, fosfatidilglicerol, lisofosfatidilcolina, PEG-fosfatidiletanolamina, Østeres lactilicos de Æcidosgrasos, estearoil-2-lactilato, estearoil lactilato, monoglicØridos succinilados, Østeres de ÆcidotartÆricomono/diacetilados de
35 mono/diglicØridos, Østeres de Æcidocitrico de mono/diglicØridos, colato, taurocolato,
glicocolato, desoxicolato, taurodesoxicolato, glicodesoxicolato, colilsarcosina, caproato, caprilato, caprato, laurato, oleato, lauril sulfato, docusato y sus sales y mezclas. En al

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menos una realización, el tensioactivo iOnico se selecciona entre lecitina, Østeres
lactIlicos de Æcidosgrasos, estearoil-2-lactilato, estearoil lactilato, monoglicØridos suceinilados, Østeres del ÆcidotartÆrico mono/diacetilados demono/diglicØridos, Østeres
de Æcidocitrico de mono/diglicØridos, taurocolato, caprilato, caprato, oleato, lauril
5 sulfato, docusato y sus sales y mezclas.

Los ejemplos de tensioactivos lipófilos incluyen alcoholes; Øteres polioxietilen aiqullicos; Æcidos grasos;Østeres de ªcidos grasos de glicerol; Østeres de Æcidosgrasos de glicerol acetilados; Østeres de Æcidos grasosde alcoholes inferiores; Østeres de Æcidos grasosde
10 polietilenglicol; Østeres de Æcidos grasos depolietilenglicol glicerol; Østeres de Æcidos
grasos de polipropilenglicol; polioxietilen glicØridos; derivados de ÆcidolÆcticode mono/diglicØridos; propilenglicol diglicØridos; Østeres de Æcidos grasos de sorbitÆn;
Østeres de Æcidosgrasos de polioxietilen sorbitân; copolimeros en bloque de polioxietileno-polioxipropileno; aceites vegetales transesterificados; esteroles; derivados
15 de esteroles; Østeres de azUcares; Øteres de azücares; sucroglicØridos; aceites vegetales
polioxietilenados; aceites vegetales hidrogenados polioxietilenados; y sus mezclas.

Al igual que los tensioäctivo hidrófilos, los tensioactivos lipOfilos pueden ser mezclas de reacciOn de polioles y Æcidos grasos,glicØridos, aceites vegetales, aceites vegetales
20 hidrogenados y esteroles.

En ciertas realizaciones, los tensioactivos lipOfilos incluyen uno o mÆsseleccionados del
grupo comprendido por Æcidos grasos;Østeres de Æcidos grasosde alcoholes inferiores;
Østeres de Æcidos grasos de polietilenglicol glicerol; Østeres de Æcidos grasos de
025 polipropilenglicol; polioxietilen glicØridos; Østeres de Æcidosgrasos de glicerol; Østeres de
Æcidos grasosde glicerol acetilados; derivados de ªcido lÆctico demono/diglicØridos;
Østeres de ªcidos grasos de sorbitÆn;Østeres de Æcidos grasos de polioxietilensorbitÆn; copolImeros en bloque de polioxietileno-polioxipropileno; aceites vegetales polioxietilenados; aceites vegetales hidrogenados polioxietilenados; y mezclas de
30 reacción de polioles y Æcidos grasos, glicØridos, aceites vegetales, aceites vegetales
hidrogenados, esteroles y sus mezclas.

En ciertas otras realizaciones, los tensioactivos lipófilos incluyen uno o mÆs
seleccionados del grupo comprendido por Østeres de Æcidosgrasos de alcoholes
35 inferiores; Østeres de Æcidos grasos de polipropilenglicol; Østeres de Æcidosgrasos de
prolilenglicol: Østeres de Æcidosgrasos de glicerol; Østeres de Æcidosgrasos de glicerol acetilados; derivados de Æcido lÆcticode mono/digliceridos; Østeres de Æcidosgrasos de

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sorbitªn; aceites vegetales polioxietilenados; y sus mezcias. Entre los Østeres de Æcidos grasos de glicerol, los Østeres pueden ser mono o diglicØridos, o mezcias de mono y diglicØridos, donde la porciOn Æcido graso es un Æcido grasoC6 a C22.

Otras realizaciones inciuyen tensioactivos iipOfilos que son la mezcla de reacciones de polioles y Æcidos grasos, gliceridos,aceites vegetales, aceites vegetales hidrogenados y
esteroles. Los ejempios de los polioles son polietilenglicol, sorbitol, propilenglicol, pentaeritritoi y sus mezcias.

10 Se pueden usar combinaciones de los potenciadores de la solubilidad (es decir
tensioactivos). Los ejempios de Østeres de Æcidos grasos de macrogol ütiles comb
potenciadores de la solubilidad incluyen GELUCIREfi 50/13 y GELUCIREfi 44/14. En
. al menos una realizaciOn el potenciador de la solubilidad es GELUCIREfi 50/13. El
potenciador de la solubilidad puede estar presente en una cantidad entre
15 aproximadamente 0,1% y aproximadamente 70% en peso del peso de la micropartleula,
incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci potenciador de la solubilidad estª presente en una cantidad entre aproximadamente 1% y aproximadamente 50%, incluidos todos los valores y rangos intermedios; en otras
realizaciones entre aproximadamente 10% y aproximadamente 30%, incluidos todos los
20 valores y rangos intermedios; y aun en otras realizaciones entre aproximadamente 15% y
aproximadamente 25% en peso de la micropartIcula, incluidos todos los valores y rangos intermedios. En al menos una realización el potenciador de la solubilidad estÆ presente
en una cantidad de aproximadamente 20% en peso de la micropartIcula.

1025 Se contempia que en algunas realizaciones se pueden usar en las microparticuias, uno o
mÆs de otros excipientesfarmacØuticamente aceptabies compatibles con los objetivos de
la presente invención, como un iubricante, un aglutinante, un modificador del pH, un
relieno y/o un deslizante.

30 Los procesos para elaborar las micropartIculas que contienen fÆnnaco de ciertas
realizaciones de la presente invención por esferonización no estÆn restringidos a la
tecnoiogIa CEFORMTM y tambiØn se puede usar cualquier otra tecnologIa que dØ como resultado la formación de las micropartIculas compatibles con los objetivos de la presente invención. Por ejemplo, las micropartIculas de ciertas realizaciones de la invenciOn
35 tambiØn se pueden elaborar por extrusiónlesferonizaciOn, granuiacion o peletización.

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ExtrusiónlesferonizaciOn es un proceso multipasos usado para hacer particulas esfØricas de tamaflo uniforme. La tØcnica ofrece la capacidad de incorporar niveles altos de ingredientes activos sin producir particulas excesivamente grandes. Los pasos principales del proceso son:
Mezcla en seco de los ingredientes para lograr una dispersion de polvos homogØnea; Amasado en hümedo usando por ejemplo un granulador de alto cizallamiento en hiimedo para formar particulas en forma de varilla de diÆmetrouniforme;
Extrusion para formar particulas en forma de varifla de diªmetro uniforme;
Esferonización para redondear las varillas en particulas esfØricas;
10 Tamización para lograr la distribución estrecha de tamaflos de la partleula deseada.

El recipiente de mezcla usado para la mezela en seco puede set de cualquier tamano y
forma compatible con ci tamaæo de la formulación que se va a producir. Por ejemplo, se pueden usar dispositivos de mezcla comercialmente disponibles como los mezcladores
15 pianetarios, los mezcladores de alto cizallamiento o los mezcladores de dos conos. Si se
van a preparar cantidades relativamente pequeflas de formulación, un simple mortero con
su mano pueden ser suficientes para mezclar los ingredientes. El tipo de recipiente de mezcla serÆ evidente para untØcnico con experiencia en el area farmacØutica. La masa humedecida fonnada por amasado en hümedo en un equipo de granulacion convencional
20 se extruye a travØs de una malla perforada para producir filamentos cilIndricos. El
orificio de las mallas puede determinar el diÆmetrode los filamentos. En este proceso se
puede usar un orificio que varIe de aproximadamente 0,2 mm a aproximadamente 3 mm, incluidos todos los valores y tangos intermedios. En al menos una reaiización que utiliza
este proceso, ci orificio varla de aproximadamente 0,4 mm a aproximadamente 2 mm,
025 incluidos todos los valores y rangos intermedios. La extrusion se puede ilevar a cabo
usando extrusoras de tornillo, de doble tornillo, del tipo "cedazo y cesta", "extrusora de
rodillo", "extrusora de pisones" o cualquier otro medio farmacØuticamente aceptable para producir filamentos cilIndricos. En ciertas realizaciones que utilizan este proceso de extrusióiilesferonizaciOn, se usa una extrusora coaxial de tornillo doble. El dispositivo de
30 esferonización comprende un cilindro hueco con una placa rotatoria horizontal. Los
filamentos se rompen en segmentos cortos que se transforman en particulas esfØricas o cuasiesfØricas en la superficie superior de la placa rotatoria a una velocidad que varia de aproximadamente 200 rpm a aproximadamente 2.000 rpm, incluidos todos los valores y rangos intermedios. Las particulas se pueden secar de cualquier manera
35 farmacØuticamente aceptable, como pot ejemplo por secado en aire en una condición
estÆtica. Las particulas se usan como estÆno se recubren para obtener grÆnulospara usar
en los comprimidos, las cÆpsulas, bolsitas u otrasformulaciones farmacØuticas.

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Un ejemplo profØtico de una forniulación de extrusión!esferonización que comprende el bromhidrato de bupropion puede ser la siguiente: En este ejemplo, el bromhidrato de bupropion puede estar presente en una cantidad entre aproximadamente 1% y
5 aproximadamente 80% p/p, incluidos todos los valores y rangos intermedios. En ciertas
realizaciones dentro de este ejemplo, el bromhidrato de bupropion estÆpresente en una cantidad entre aproximadamente 1% y aproximadamente 50% p/p; en otras realizaciones entre aproximadamente 10% y aproximadamente 30%; y aim en otras realizaciones, aproximadamente 10% p/p. En este ejemplo, el relleno puede estar presente en una
10 cantidad entre aproximadamente 0% y aproximadamente 80% p/p, incluidos todos los
valores y rangos intermedios. En ciertas realizaciones de este ejemplo, el relleno estÆ presente en una cantidad entre aproximadamente 10% y aproximadamente 60%; y en
otras realizaciones, aproximadamente 40% p/p. En este ejemplo, la celulosa microcristalina puede estar presente en una cantidad entre aproximadamente 10% y
15 aproximadamente 90% p/p, incluidos todos los valores y rangos intermedios. En ciertas
realizaciones de este ejemplo, la celulosa microcristalina estÆpresente en una cantidad
entre aproximadamente 10% y aproximadamente 70%; y en otras realizaciones, entre aproximadamente 20%. y aproximadamente 50% p/p. En este ejemplo, el agiutinante
puede estar presente en una cantidad entre aproximadamente 0% y aproximadamente
20 10% p/p, incluidos todos los valores y rangos intermedios. En ciertas realizaciones de
este ej emplo, ci agiutinante estÆpresente en una cantidad entre aproximadamente 1% y aproximadamente 8%; y en otras realizaciones, entre aproximadamente 2% y
aproximadamente 4% p/p. En este ejemplo, el agua puede estar presente en una cantidad

10 entre aproximadamente 10% y aproximadamente 80% p/p, incluidos todos los valores y
25 rangos intermedios. En ciertas realizaciones de este ejemplo, el agua estÆpresente en una
cantidad entre aproximadamente 15% y aproximadamente 70%; y en otras realizaciones,
entre aproximadamente 20% y aproximadamente 50% p/p. Los rellenos adecuados que
se pueden usar en este ejemplo incluyen, pero no exclusivamente, fosfato dibÆsicode
calcio, fosfato tricªlcico, carbonato de calcio, almidón (como almidones de maIz, papa y
30 arroz), almidones modificados (como carboximetilalmidOn, etc.), celulosa
microcristalina, sacarosa, dextrosa, maltodextrinas, lactosa y fructosa. Los lubricantes adecuados que se pueden usar en este ejemplo incluyen, pero no exclusivamente,
estearatos metÆlicos(como estearatos de calcio, magnesio o cinc), Æcidoesteó.rico, aceites vegetales hidrogenados, talco, aimidón, aceite mineral ligero, benzoato de sodio, cloruro
35 de sodio, lauril sulfato de sodio, lauril sulfato de magnesio, estearil fumarato de sodio,
behenato de glicerilo y polietilenglicol (como CARBOWAXTM 4000 y 6000). Los antiadherentes adecuados en este ejemplo incluyen, pero no exclusivamente, al dióxido

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de silicio coloidal. Los aglutinantes adecuados en este ejemplo incluyen, pero no exciusivamente, etilcelulosa, un poilmero de polimetacrilato, alcohol polivinilico, polivinilpirrolidona, copolImero de polivinilpirrolidona-acetato de vinilo (por ejemplo, KOLLIDONfi VA64) hidroxietilcelulosa, hidroxipropilmetilcelulosa de baj o peso
molecular (por ejemplo, viscosidad de aproximadamente 1-50 cp a aproximadamente
20°C; aproximadamente 2-12 cp a aproximadamente 20°C; o aproximadamente 4-6 cp a aproximadamente 20°C), polimetacrilatos de hidroxipropilcelulosa y sus mezclas.

Las micropartIculas que contienen fÆrmacoformadas por extrusión/esferonizaciOn en este
10 ejemplo profØtico se pueden producir usando polimeros anfifihicos reticulados mediante
los pasos siguientes: (a) mezcla de uno o mÆs polimerosanfifIlicos reticulados con bromhidrato de bupropion y opcionalmente otros excipientes farmacØuticos para obtener
una mezela uniforme en forma de polvo seco al cual se agrega una cantidad adecuada de 11quido para obtener una consistencia pastosa; (b) extrusion de la mezcla obtenida en el
15 paso (a) a travØs de una malla perforada para obtener filamentos cilindricos con la
longitud y el diÆmetrodeseados; (c) esferonización de los filamentos para obtener un producto en forma de multiparticulados esfØricos; (d) secado del producto; y (e)
colocación opcional de un fªrmaco sobre la superficie de las micropartIculas. "Poilmero anfifilico reticulado" hace referencia en este ejemplo a los polimeros que presentan
20 caracteristicas de hinchabilidad en todo el intervalo pH de las soluciones acuosas y
tambiØn en disolventes o mezclas disolventes con caracteristicas de polaridad diferentes.
Los polimeros pueden ser reticulados ya sea flsicamente a travØs de la interpenetración de
las mallas macromoleculares, o qulmicamente, mostrando por lo tanto puntos de union
entre las cadenas macromoleculares. Los ejemplos no limitantes de dichos polimeros
025 incluyen polivinilpirrolidona reticulada, carboximetilcelulosa sódica, glicolato sódico de
almidón y dextranos. Los, excipientes opcionales incluyen dispersantes, emulsionante, humectantes y colorantes. La expresión "mezcla uniforme" en este ejemplo significa que
los componentes de la mezcla se dispersan uniformemente en la formulación mediante un proceso de mezcla que asegura la distribuciOn uniforme de cada componente. Un tiempo
30 de mezcla razonable puede variar de aproximadamente 1 a aproximadamente 60 minutos,
incluidos todos los valores y rangos intermedios, usando uno de los equipos de mezcla convencionalmente utilizados para la mezcla en seco de los polvos (por ejemplo,
mezcladoras en "V", de cuerpo fijo, de cuerpo rotatorio y sigma). El tØrmino "lIquido"
en este ejemplo signiflea eualquier sustancia lIquida o mezcla (solución o emulsion) de
35 lIquidos de uso farmacØutico normal capaz de humedecer la mezcla de polvos, como por
ejemplo agua, soluciones acuosas con diferente p1-I, disolventes orgÆnicos de uso farmacØutico normal (por ejemplo, alcoholes, disolventes clorados) y aceites. Entre los

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aceites y los tensioactivos que se pueden usar en este ejemplo estÆn:los aceites naturales,
ya sea saturados o insaturados (aceites de oliva, manI, soja, maIz, coco, palma, sØsamo y
similares); los mono, di y triglicØridos semisintØticos y sintØticos, que contienen Æcidos
grasos saturados y/o insaturados y sus derivados polihidroxietilados (triglicØridos
cÆprico-caprilico [MYGLIOLTM,CAPTEXTM, LABRAFACTM, LIPOTM], los trigliceridos
polihidroxilados saturados o insaturados de diversas clases [LABRAFILTM,
LABRAFACTM Hydro, GELUCIRETM]); las ceras liquidas (miristato de isopropilo,
caprinato de isopropilo, caprilato de isopropilo, laurato de isopropilo, palmitato de
isopropilo, estearato de isopropilo); los Østeres de Æcidos grasos (oleatode etilo, oleato de
10 oleilo); los aceites de silicona; polietilenglicoles (PEG 200, PEG 400, PEG 600, PEG
1.000, y asI sucesivamente); los glicØridos poliglicOlicos (por ejemplo LABRASOLTM);
los poliglicoles (propilenglicol, tetraglicol y etoxidiglicol (TRANSCUTOLTM), los
Østeres de Æcidos grasosde sorbitÆn (porejemplo SPANfi, ARLACELfi, BRIJfi), los
Østeres de Æcidos grasosde polioxietilensorbitân (por ejemplo TWEENfi, CAPMULfi,
15 LIPOSORBfi), los copoilmeros de óxido de polipropileno-óxido de polietileno
(Poloxamer), los Østeres del polietilenglicol (PEG)-glicerol (LABRASOLfi,
LABRAFILfi), los Østeres de PEG y ÆcidosalifÆticoso alcoholes de cadena larga (por ejemplo CREMOPHORfi), los Østeres poligliceridos (PLUROLfi), los Østeres sacÆridos
y de Æcidosgrasos (sucro-Østeres) y sus mezelas. AdemÆs, se puedenusar tensioactivos
20 anionicos (por ejemplo lauril sulfato de sodio, estearato de sodio, oleato de sodio) o
tensioactivos eatiónicos (por ejemplo tricetol), asi como lecitinas, fosfolipidos y sus derivados semisintØticos o sintØticos. TambiØn el bromhidrato de bupropion y/o los excipientes Se pueden disolver, dispersar y/o emulsionar en dichos lIquidos.

25 En una realización particular formada por un proceso de extrusiónbesferonización del
ejemplo profØtico descrito anteriormente, el liquido humectante compreride un sistema aceite/tensioactivo en donde se disuelve o se dispersa el bromhidrato de bupropion opcionalmente emulsionado con una fase acuosa. La cantidad de liquido con respecto al sólido usada en la preparación de la mezcla puede variar de aproximadamente 1% a
30 aproximadamente 80% en peso, incluidos todos los valores y rangos intermedios. Como
un ejemplo profØtico de esta realización, una mezcla de bromhidrato de bupropion y KOLLIDONTM CL en una relaciOn igual a aproximadamente 1:3 en peso se muele conjuntamente obteniØndose la mezcla en forma de polvo con aproximadamente 100% de
la granulometrIa inferior a aproximadamente 50 micras. La mezcla Se humedece usando
35 agua desmineralizada que contiene KOLLIDONTM 25 (polivinilpirrolidona, BASF) en
una solución al 3% p/p. Se lieva a cabo la extrusiOn forzando la masa humedecida a
travØs de una roscadora que tiene un diametro de los orificios igual a aproximadamente 1

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mm. Los parÆmetrosoperativos en este ejemplo profØtico pueden ser los siguientes: velocidad de flujo de polvo: aproximadamente 4,5 kg/h; velocidad de flujo del lIquido: aproximadamente 4,1 kg/h; esfuerzo torsional: aproximadamente 27%; temperatura de la eabeza: aproximadamente 46°C; y la velocidad de rotación del tornillo: aproximadamente
5 140 rpm. Los filamentos de extrusion se procesan luego en un esferonizador ajustado a
una velocidad igual a aproximadamente 1.000 rpm durante aproximadamente 2 minutos. DespuØs las micropartIculas obtenidas se secan en un lecho fluido durante
aproximadamente 2 horas a una temperatura maxima igual a aproximadamente 59°C. Al final del secado, ci producto se descarga y se tamiza mecÆnicamente separando la
10 fraceiOn que varla de aproximadamente 0,7 mm a aproximadamente 1,2 mm.

Otro ejemplo profØtico de una realización de las micropartIculas que contienen fÆrmaco
de la invención formadas por un proceso de extrusión/esferonizaciOn, usa una resina cargada, cuyos pasos pueden comprender: (a) agregar la resina cargada, el bromhidrato
15 de bupropion y otros excipientes, a un recipiente de mezcla; (b) mezelar los ingredientes
para obtener una mezcla uniforme; (c) agregar una soluciOn de granulaciOn o un liquido capaz de humedecer la mezcla seca. Se incluyen los lIquidos que dan lugar a la
conversion de la mezcla de polvos secos en una granulación hümeda que soporta la
extrusion y esferonización posteriores (marumerización). TIpicamente, se emplean agua
20 o soluciones acuosas. Se pueden incluir alcoholes, tIpicamente etanol o isopropanol, con
el agua de granulación para mejorar la maniobrabilidad de la granulación. En otra
realización de esta invención, uno o mªs de los componentes de la formulaciOn se
disuelven primero en agua y esta solución se usa para producir la granulación hümeda.
Un principio activo o un excipiente que estÆ presenteen una concentración muy baja se
1025 puede disolver o suspender inicialmente en el disolvente de granulaciOn para asegurar la
distribución mÆs uniforme en toda la formulación. (d) granular la mezcla hasta que
resulte una granulación uniforme; (e) extrudir la granulación hümeda a travØs de un tamiz
para producir filamentos de granulación; (f) esferonizar los filamentos de la granulacion
para producir inultiparticulados esfØricos; y (g) recoger y secar los multiparticulados
30 esfØricos. Por "resina cargada" se quiere dar a entender en este ejemplo un polimero con
grupos funcionales ionizables que Se torna ütil en la realización de esta invenciOn. Esto abarca ampliamente cualquier poilmero que al ionizarse, es capaz de producir cadenas polimØricas catiónicas o aniónicas y que soporta esferonización. Tipicamente de aproximadamente 10% a aproximadamente 70% en peso del multiparticulado esfØrico es
35 resina cargada. Ejemplos no limitantes de estas resinas cargadas incluyen poliestiren
sulfonato de sodio (por ejemplo, AMBERLITE IRP-69TM); la sal de cloruro de la resina colestirarnina USP (por ejemplo, AMBERLITE IRP276TM); la forma Æcidade Æcido

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metracrIlico-divinil benceno (por ejemplo, AMBERLITE IRP64TM);
carboxipolimetilenos (por ejemplo, CARBOPOLTM 974P y CARBOPOLTM 934P), y poliacrilato de sodio (por ejemplo, AQUAKEEPTM J-550). Para que la resina pueda mantener ci grado de ionización deseado, se pueden incluir los agentes que producen un ambiente Æcido o bÆsico durante la granulaciony la esferonización en la formulación. Entre los grupos de compuestos que pueden ejercer este efecto estÆn losÆcidos,las bases y las sales de Æcidosy bases como ÆcidoadIpico, ÆcidocItrico, ÆcidofumÆrico,Æcido tartÆrico,Æcido sucelnico, carbonato de sodio,bicarbonato de sodio, citrato de sodio, acetato de sodio, f’osfatos de sodio, fosfatos de potasio, fosfato de amonio, óxido de magnesio, hidróxido de magnesio, tartrato de sodio y trometamina. Se pueden agregar ciertos compuestos a la granulación para proporcionar ci grado adecuado de hidratación de la resina cargada, el medicamento y los excipientes. Estos hidratantes inciuyen aziicares como lactosa, sacarosa, manitol, sorbitol, pentaeritritol, glucosa y dextrosa. TambiØn se pueden usar polImeros como polietilenglicol asI como tensioactivos y otras sales orgÆnicas e inorgÆnicas para modularha hidrataciOn del polimero.

En otro ejemplo profØtico, se pueden obtener multipartieulados que contienen bromhidrato de bupropion del modo siguiente:
Componente Porcentaje p/p
Bupropion HBr aproximadamente 8,7
Fosfato disódico aproximadamente 7,0
Fosfato monosódico aproximadamente 1,7
Dodecil sulfato de sodio aproximadamente 21,7
Cloruro de sodio aproximadamente 17,4
Povidona 29-32K aproximadamente 8,7
AMBERLITE IRP-69 aproximadamente 34,8
Hidroxianisol butilado aproximadamente 0,0002

En este ejemplo profØtico, aproximadamente 5,75 kg de la formulación anterior se mezelan en un mezclador pianetario durante aproximadamente 15 minutos. El hidroxianisol butilado se disuelve en aproximadamente 60 cc de etanol y se agrega agua para ilevar la solución a un volumen final de aproximadamente 133 cc. Esta solución se agrega al mezclador planetario durante un perlodo de aproximadamente dos (2) minutos. El mezclador se granula despuØs con siete allcuotas de aproximadamente 250 cc de agua agregadas durante un perIodo de aproximadamente quince minutos. La granulacion asI formada se extruye a travØs de un tamiz de 1,0 mm y las alicuotas se esferonizan por marumerizaciOn a aproximadamente 1.200 rpm durante aproximadamente 10 minutos

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cada una. DespuØs los tnultiparticulados esfØricos forniados se secan a aproximadamente 50°C durante aproximadamente 24 horas.

Otra realización de esta invención implica la producción de micropartIculas que
contienen farmaco en forma de ’perlas’. Las perlas se pueden fabricar mezelando el bromhidrato de bupropion eon uno o mÆsexcipientes farmacØuticos en forma fundida; la masa fundida Se hace pasar a la fuerza a travØs de una boquilla sometida a una vibración;
las perlas formadas se dejan caer en una tone a contracorriente a un gas; y las perlas
sOlidas se recogen en el fondo de la tone. En este ejemplo, la eantidad de bromhidrato de
10 bupropion puede variar de aproximadamente 5% a aproximadamente 95% en peso,
incluidos todos los valores y rangos intermedios; y en ciertas realizaciones, de aproximadamente 40% a aproximadamente 60% en peso, incluidos todos los valores y rangos intermedios. Los aditivos que permiten inducir la cristalización del producto superenfriado en este ejemplo se pueden elegir entre los siguientes: aleoholes grasos
15 como: alcohol cetIlico’alcohol estearIlico, Æcidosgrasos como: ªcido esteÆrico,Æeido
palmItico, Østeres de glicerol como: palmitoestearato de glicerol, estearato de glicerol
(por ejemplo, PRECIROLTM), behenato de glicerol (por ejemplo, COMPRITOLTM),
aceites hidrogenados como: aceite de ricino hidrogenado (pot ejemplo,. CUTINATM HR), sales de ªcidos grasos como: estearato de calcio o magnesio, polioles como: manitol,
20 sorbitol, xilitol, ceras comb: cera blanca, cera carnauba, cera de parafina,
polioxitilenglicoles de alto peso molecular y polioxietilenos esterificados como:
distearato de PEG-32 y distearato de PEG-150. A estos aditivos de cristalización puede
ser deseable en este ejemplo agregaries polImeros que son solubles o dispersables en la
masa fundida y que proporcionan una disolución controlada y regulable de las perlas
025 cuando se usan, cuyos ejemplos incluyen: derivados de eelulosa (hidroxipropilcelulosa,
hidroxipropilmetilcelulosa, hidroxietileelulosa, etileelulosa, earboximetilcelulosa),
resinas aerIlicas (por ejemplo, EUDRAGITfi), acetatos polivinilicos (por ejemplo, RHODOPASfi), polialquileno (etileno, propileno), polilÆctieo,anhIdrido maleico, resinas
de silicona y sus mezclas. AdeinÆs,se pueden agregar aditivos inorgÆnicospara acelerar
30 la solidificación de los principios activos, cuyos ejemplos incluyen: sIlices, óxidos
inorgÆnicoscomo óxido de titanio o de hierro, fosfatos, carbonatos, areillas y talco.
AdemÆs, se puedeagregar un agente de superficie para mejorar la dispersion de la
sustancia activa en el aditivo de eristalización, cuyos ejemplos incluyen: Østeres de
sorbitol, polisorbatos de polioxietileno (por ejemplo, TWEENfi) y glicoles como
35 glicerina o propilenglicol. El proceso para la preparaeión de las perlas comprende
preparar una masa fundida del brornhidrato de bupropion eon uno o mÆs excipientes.
Esta masa fundida se puede preparar fundiendo por separado diversos constituyentes y

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luego mezclÆndoloso fundiendo la mezcla de los constituyentes y agregando los posibles compuestos insolubles al final de la fusion para obtener una masa homogØnea. El tØcnico con experiencia en el Area elige la naturaleza de los constituyentes de la masa fundida la
que se considera en función de la compatibilidad de los constituyentes, la viscosidad de la
5 mezela de los constituyentes, el diÆmetrode ía boquilla, ía hidrofihicidad del principio
activo, la tension superficial del principio activo, ci tamauio de particula de los aditivos insolubles, la velocidad de flujo de la boquilla, la temperatura de la terre, su altura y,
sobre todo, el tamaflo deseado de las perlas, la proporción de bromhidrato de bupropion
que se va a incluir y el tiempo de liberaciOn del principio activo deseado.

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Los procedimientos alternativos diferentes de ía extrusion o la esferonización para
preparar mieropartIculas que contienen fÆrmaco puedenincluir granuiaciOn hümeda,
. granulaciOn en disolvente y granulación por fusion. Todas estas tØdnicas implican ía
adición de un aglutinante inactive para agregar las particulas mÆspequeflas en granules
15 mÆsgrandes. Per ejemplo, la granulación himeda y la granulación en disolvente
implican la adición de un aglutinante lIquido que agregue los materiales activos y los excipientes en grnulos. DespuØs de la granulación, se puede eliminar e1 liquido
mediante otro paso de secado. La granulación por fusion es similar a la granulación
hümeda, pero usa un material sólido de bajo punto de fusion come aglutinante. El
20 aglutinante sOiido en la granulación per fusion se funde y actüa come un aglutinante
liquido agregando de ese mode al principio active y los excipientes en polvo en granules.
De ese mode, el aglutinante se puede incorporar en los grÆnutoscuando los granules se enfrIan.

25 Ciertas realizaciones de la presente inveneión inciuyen microparticulas elaboradas por un
proceso para producir granules per graxiulacion en rotomelt que comprende la mezcla del bromhidrato de bupropion y de un material excipiente en polvo con un punto de fusiOn mayor que el bromhidrato de bupropion en una zena en la que ambos materiales en polvo
se mantienen en un estade fluidizado mediante una corriente ascendente de gas en un
30 aparato que tiene un disco horizontal que gira rÆpidamente ubicadodentro de un
recipiente vertical que tiene una superficie inferior; en donde dicho disco que gira rÆpidamenteestÆubicado sobre la superficie inferior del recipiente vertical en donde
dicho gas estÆa una temperatura suficiente para provocar ía fusion al menos parcial del bromhidrato de bupropion haciendo de ese mode que dichos materiales en polvo se
35 agreguen y formen grÆnulos. Otras realizaciones de ía presente invenciOn inciuyen
rnicropartfcuias elaboradas mediante un proceso para producir grÆnulos pergranulación
en rotorneit que comprende mezclar ci material aglutinante en polvo y ci bromhidrato de

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bupropion, donde el bromhidrato de bupropion tiene un punto de fusion mayor que el material aglutinante en polvo en una zona en la que ambos materiales en polvo se
mantienen en un estado fluidizado mediante una corriente ascendente de gas en un
aparato que tiene un disco horizontal que gira rÆpidarnente ubicado dentro deun
5 recipiente vertical que tiene una superficie inferior; donde dicho disco que gira
rÆpidamente estÆ ubicado sobre la superficieinferior del recipiente vertical donde dicho
gas estÆa una temperatura suficiente para provocar la fusion al menos parcial del material aglutinante haciendo de ese modo que dichos materiales en polvo se agreguen y formen granulos.
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En la granulacion en rotomelt, uno de los polvos de alimentación debe tener un punto de fusion inferior que el otro polvo para servir como aglutinante. Los polvos de alimentaciOn
se introducen en un recipiente vertical con un disco horizontal que gira ubicado en ci
fondo del recipiente. El polvo se mantiene en estado fluidizado mediante al menos una
15 corriente de aire filtrado que se hace circular desde ci fondo del recipiente vertical a
travØs de una o mÆs entradas. DespuØs sehace girar ci disco horizontal giratorio mientras
el aire provisto para fluidizar ci polvo se mantiene a una temperatura suficiente para
ablandar o fundir el polvo de menor punto de fusion. La temperatura a la cual se debe calentar el aglutinante para que se ablande Sc puede determinar empIricamente
20 observando la formaciOn de grÆnulosa diversas temperaturas para diversos aglutinantes.
En la actualidad se cree que las temperaturas de 3°C a 5°C por debajo del punto de fusiOn
o del intervalo de fusion, incluidos todos los valores y rangos intermedios, proporcionan suficiente ablandamiento para dar lugar a la formaciOn de granuios. El polvo de menor
punto de fusiOn actiia despuØs como un aglutinante para promover la agregaciOn de las
 25 partIculas de polvo en grÆnulos. Los polvos adecuados para usar en la granulaciOn con
rotomelt tienen un tamaflo de diÆmetro en ci rangoentre aproximadamente 5 micras y aproximadamente 150 micras; incluidos los valores y rangos intermedios, y en ciertas realizaciones tienen un tamaflo de diÆmetro en el rangoentre aproximadamente 35 micras
y aproximadamente 80 micras. La temperatura a la que se expondrÆnlos componentes
30 depende del aglutinante empleado para agregar los polvos. En general, ci punto de fusiOn
del aglutinante estÆ por encimade aproximadamente 30°C; y en ciertas realizaciones estÆ por debajo de aproximadamente 100°C.

Los polvos usados en estas micropartIcuias preparadas por granulación en rotomelt se
35 pueden transformar en grÆnulos por al menosdos mecanismos de granulaciOn
alternativos. El primer mecanismo para la formación de grÆnulos utiliza un aglutinante particulado de mayor tamaflo y un polvo particulado de menor tamaflo. DespuØs se elcva

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la temperatura durante la granulación en rotomelt solo hasta ci punto en el que la
superficie externa de las partIculas de aglutinante se vuelve pegajosa. A medida que el segundo material en polvo de un tamaho menor entra en contacto con la superficie
pegajosa forma una microcapa sobre la superficie de la partIcula de aglutinante. Este
5 mecanismo de granulaciOn da lugar a grÆnulosque tienen una distribución de tarnafio
similar a la de las particulas originales de aglutinante empleadas. Alternativamente, la granulaciOn en rotomelt puede lievarse a cabo a una temperatura a la cual el aglutinante actIia como un cemento que forma puentes en los espacios entre las partleulas sin fundir (esto Se denomina aglomeraciOn). Este mecanismo da lugar a la formación de grÆnulos
10 donde los componentes se entremezclan. Para cada aglutinante usado ci mecanismo se
puede controlar principalmente mediante la temperatura a la cual se realiza la granulación
en rotomelt. Los tØcnicos con experiencia en el drea apreciarÆn quelos grªnulos
formados se pueden observar por microscopia electrónica para determinar el tipo de
proceso de granulación que ocurre. Si se desea un tipo particular de grªriulo, se pueden
15 variar las condiciones o los materiales de partida del proceso para producir los grÆnulos
deseados.

En al menos una realizaciOn de la presente invención, ci bromhidrato de bupropion se
funde para actuar como un aglutinante en el proceso de granulaciOn en rotomelt. Los
20 ejemplos de excipientes adecuados incluyen los seleccionados entre los siguientes:
rellenos, lubricantes, deslizantes y antiadherentes. Los rellenos adecuados incluyen, pero
no exclusivamente, fosfato dibÆsicode calcio, fosfato tricÆlcico,carbonato de calcio,
almidOn (Como almidones de maiz, papa y arroz), almidones modificados (Como carboximetilalmidón, etc.), celulosa microcristalina, sacarosa, dextrosa, maltodextrinas,
25 lactosa y fructosa. La cantidad de aglutinante adicionada para agregar las partIculas en
granulos puede variar entre aproximadamente 10% p/p y aproximadamente 80% p/p, incluidos los valores y rangos intermedios; y en ciertas realizaciones entre
aproximadamente 30% p/p y aproximadamente 70% p/p de los materiales en polvo en la granulación en rotomelt. El porcentaje en peso restante para proporcionar un total de
30 aproximadamente 100% p/p puede ser uno o mÆs principiosactivos farmacØuticos en
polvo adecuados. Opcionalmente la granulaciOn en rotomelt tambiØn puede contener de aproximadamente 0% a aproximadamente 60% p/p, incluidos los valores y rangos intermedios, de uno o mÆsexcipientes en polvo donde el peso total de todos los
materiales en polvo equivale a aproximadamente 100% p/p. El aglutinante usado en estas
35 realizaciones de la invención puede set un polvo seco farmacØuticamente aceptable que
tiene un tamafto de particula que varla entre aproximadamente 5 p.m y aproximadamente
150 jim, incluidos todos los valores y rangos intermedios; y en ciertas realizaciones

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dentro de un rango de aproximadamente 35 nn a aproximadamente 80 rim. Los aglutinantes adecuados para la granulación en rotomelt son aglutinantes en polvo de bajo punto de fusion, cuyos ejemplos incluyen: polietilenglicol 4000, polietilenglicol 6000, Æcido esteÆricoy ceras de bajo punto de fusion. Las ceras adecuadas de bajo punto de
fusion incluyen, pero no exciusivamente, monoestearato de glicerilo, sebo hidrogenado, alcohol miristulico, ªcido mirIstico, alcohol estearilico, monoglicØridos sustituidos, diglicØridos sustituidos, trigliceridos sustituidos, cera blanca de abeja, cera carnauba, cera
de ricino, cera de Japón, monoglicØridos acetilados y sus combinaciones. Los
aglutinantes pueden tener un punto de fusion entre aproximadamente 30°C y
10 aproximadamente 100°C, incluidos todos los valores y rangos intennedios; y en ciertas
realizaciones entre aproximadamente 40°C y aproximadamente 85°C.

Dc acuerdo con un ejemplo profØtico de estas realizaciones preparadas mediante un
proceso de granulaciOn en rotomelt, se mezclan en seco aproximadamente 320 g de
15 bromhidrato de bupropion y aproximadamente 80 g de PEG 8000 y se vierten en una
camara Glatt 1.1 ajustada como un granulador rotatorlo con una placa longitudinal. La temperatura de entrada del aire se fija a aproximadamente 60°C y la cÆmaradel producto
Sc calienta aproximadamente a 50T. La mezcla se fluidiza a aproximadamente 120
in3/h y la placa friccional se fija a aproximadamente 900 rpm. La temperatura de la
20 cÆmara del productose eleva a aproximadamente 60°C y despuØs se reduce gradualmente
a aproximadamente 20°C durante un perlodo de aproximadamente 20 minutos, durante el
cual se logra la esferonizaciOn.

Otras realizaciones de la invenciOn implican la formación de una micropartIcula que tiene
025 un nücleo que contiene bromhidrato de bupropion y un compuesto que es de sabor dulce
y que tiene un calor de disoluciOn negativo. Los ejemplos de los compuestos que se
clasifican en esta categorla incluyen manitol y sorbitol. TanibiØn pueden funcionar los
azücares o los eduicorantes artificiales a los cuales se les ha agregado, por ejemplo,
mentol. TambiØn se pueden colocar un aglutinante y/o otro excipiente dentro del nücleo.
30 La cantidad de edulcorante usada puede depender de varios factores incluidos el tamafio
de las microparticulas resultantes, ci tamafio o el volurnen del comprimido resultante, la solidez del microparticulante de la micropartIcula recubierta, la velocidad a la cual se desintegrarÆ el comprimido en la boca,el grado de dulzura impartida por el edulcorante particular usado, en la micropartIcula o en el comprimido, o ambos, y de la cantidad de
35 fÆrmacousada y similares. Por ejemplo, las micropartIculas particularmente resistentes
pueden tener menor probabilidad de romperse durante la masticación y/o la compresión.
For consiguiente, se puede reducir la cantidad de material proporcionado para proteger

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contra la liberación del material de sabor desagradable. En otros casos se puede usar una cantidad relativa mayor de compuesto edulcorante. En general, la cantidad de material edulcorante usada variarÆ entremªs de cero y aproximadamente 80% del peso de las microparticulas resultantes, incluidos todos los valores y rangos intermedios. El
5 edulcorante y el bromhidrato de bupropion se pueden combinar de cualquier manera
conocida, como por ejemplo por granulaciOn hthneda, granulaeiOn seca, aglomeración, o recubrimiento por pulverización. Por ejemplo, ci edulcorante se puede usar como un
adsorbente para el principio aetivo. Alternativamente, tambiØn se pueden mezelarjuntas simplemente las partIculas de cada uno. Asimismo, se pueden usar uno o mÆs
10 aglutinantes u otros adyuvantes en la formulación de un comprimido. Los aglutinantes en
estas realizaciones incluyen, por ejemplo: almidón (por ejemplo, en una cantidad entre
5% y aproximadamente 10%, incluidos todos los valores y rangos intermedios, como una
. pasta acuosa); almidón pregelatinizado (por ejemplo, en una cantidad de
aproximadamente 5% a aproximadamente 10%, incluidos todos los valores y rangos
15 intermedios, agregado seco al polvo); gelatina (por ejemplo, en una cantidad entre
aproximadamente 2% y aproximadamente 10%, incluidos todos los valores y rangos intermedios, como una soiución acuosa, o aproximadamente 2% en pasta de almidon); polivinilpirrolidona (por ejemplo, en una cantidad entre aproximadamente 2% y aproximadamente 20%, incluidos todos los valores y rangos intermedios, en una solución
20 acuosa o aicoholica); metilcelulosa (por ejemplo, en una cantidad entre aproximadamente
2% y aproximadamente 10%, incluidos todos los valores y rangos intermedios, como una solución acuosa); carboximetilcelulosa sódica (por ejemplo, en una cantidad entre aproximadamente 2% y aproximadamente 10%, incluidos todos los valores y rangos intermedios, como una solución acuosa); etilcelulosa (por ejemplo, en una cantidad entre
25 aproximadamente 5% y aproximadamente 10%, incluidos todos los valores y rangos
intermedios, como un alcohol o solución hidroalcoholica); poliacrilamidas (Polimero JR) (por ejemplo, en una cantidad entre aproximadamente 2% y aproximadamente 8%,
incluidos todos los valores y rangos intermedios, como una solución acuosa); poliviniioxoazoiidona (Deviex) (por ejemplo, en una cantidad entre aproximadamente 5%
30 y aproximadamente 10%, incluidos todos los valores y rangos intermedios, como una
solución acuosa o hidroalcohólica); y alcoholes polivinIlicos (por ejemplo, en una
cantidad entre aproximadamente 5% y aproximadamente 20%, incluidos todos los
valores y rangos intermedios, en soluciones acuosas). TambiØn se pueden usar otros adyuvantes para formar ci nücieo de las microparticulas de las presentes realizaciones de
35 la invención, cuyos ejemplos no limitantes incluyen: sulfato de calcio NF, fosfato
dibÆsicode calcio NF, sulfato tribÆsico decalcio NF, aimidón, carbonato de calcio,
celulosa mierocristalina, aimidones modificados, lactosa, sacarosa y similares, STA-

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RXTM, AVICELTM, SOLKAFLOCTM BW40, ªeido algfnico, EXPLOTABTM,
AUTOTABTM, goma guar, caolIn VECQUMTM y bentonita. Estos adyuvantes se pueden
usar hasta en aproximadamente 20% p/p; y en ciertas realizaciones estÆn presentes en una
cantidad entre aproximadamente 3% y aproximadamente 5% pIp, incluidos todos los
5 valores y rangos intermedios.

Como un ej emplo profØtico de estas realizaciones que tienen un nücleo que contiene bromhidrato de bupropion y un compuesto que es de sabor dulce, ci bromhidrato de bupropion se puede granular usando el procedimiento siguiente: Se disuelve
10 polivinilpirrolidona K-30 USP (aproximadamente 240,0 g) en agua destilada
(aproximadamente 1.890,0 g) con agitación. Se colocan polvo de manitol USP (aproximadamente 11,160 g) y bromhidrato de bupropion (aproximadamente 600,0 g) en
un granulador/procesador Zanchetta de 50 litros. DespuØs de una mezcla en seco inicial
de dos minutos de los polvos con la cortadora encendida y ci propulsor ajustado a
15 aproximadamente 200 rpm, la solución de polivinilpirrolidona K30 se pulveriza
lentamente en el leeho de mezcla del polvo usando un sistema de pulverización
conducido por aire. El tiempo total de granulación incluido el tiempo de adición de la soluciOn es de aproximadamente ocho minutos. El punto final de granulación se
determina visualmente y por ía consistencia del material resuitante. DespuØs ci material
20 se descarga sobre bandejas y se seca a aproximadamente 80°C utilizando aire seco
provisto durante un periodo de aproximadamente seis horas a un contenido de humedad
de no mÆs de0,08 por ciento aproximadamente. El material seco se pasa luego a travØs
de un molino de martillos (cuchillas delanteras) equipado con un tamiz U.S. N° 40 (420 micras).

Otras realizaciones de esta invención implican la granulación y ci recubrimiento
combinados del bromhidrato de bupropion en microparticulas en las que ci fÆrmacoestÆ localizado, al menos en parte, dentro del nücieo de la micropartIcula pero es capaz de iiberaciOn inmediata. Para hacer esto, se mezclan en seco primero ci bromhidrato de
30 bupropion y un desintegrante granular; despuØs se granula ci polvo obtenido, en
presencia de una mezcla de excipientes que comprenden al menos un agiutinante capaz
de unir las partleulas para dar granos; despuØs los granos asi formados se recubren puiverizÆndoloscon una suspension que comprende al menos un agente de recubrimiento
y un desintegrante de membrana; y despuØs los grÆnulos recubiertosobtenidos se secan.
35 La distinción entre la granulaciOn real y los pasos de recubrimiento es reiativamente
teOrica, en la medida en que, aunque la función principal del agiutinante usado en el paso
de granulación es unir las partIculas, no obstante ya recubre parcialmente los granos

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formados. Dc la misma manera, aunque la función principal del agente de recubrimiento usado en ci paso real de recubrimiento es coinpietar el recubrimiento final de cada uno de los granos, puede, sin embargo, unir arbitrariamente otros granos recubiertos por un mecanismo de aglomeración granular. El aglutinante y el agente de recubrimiento se
5 eligen del grupo que comprende los polimeros de celulosa y los polimeros acrIlicos. Sin
embargo, aunque ci aglutinante y el agente de recubrimiento se eligen del mismo grupo
de compuestos, difieren no obstante entre si en su función como se mencionó
previamente. Entre los polimeros de celulosa que se pueden elegir ventaj osamente estÆn etilcelulosa, hidroxipropilcelulosa (HPC), carboximetilcelulosa (CMC) e
10 hidroxipropilmetilcelulosa (HPMC) o sus mezclas. Entre los polimeros acrIlicos que se
pueden elegir ventajosamente estn el copolImero de metacrilato de amonio
(EUDRAGITfi RL o RS), el poliacrilato (EUDRAGITfi NE) y el copolImero de Æcido metacrIlico (EUDRAGITfi L o S). En al menos una realización, el aglutinante es de la misma naturaleza que ci agente de recubrimiento. Para acelerar aün mÆs la liberaciOn del
15 bromhidrato de bupropion, la suspension de recubrimiento tambiØn comprende un
permeabilizante quo, debido a sus propiedades intrinsecas de solubilidad, causa
perforación del recubrimiento de membrana, permitiendo asi la liberación del
bromhidrato de bupropion. Los ej emplos no limitantes de permeabilizantes inciuyen
povidona y sus derivados, polietilenglicol, silice, polioles y polimeros de celulosa de
20 viscosidad baja. Los polimeros del tipo de la hipromelosa, cuya viscosidad es igual a
aproximadamente 6 centipoises, se usan, por ejemplo, como polimeros de celulosa de
viscosidad baja. En al menos una realizaciOn, la mezcla en seco del polvo inicial y la granulación, el recubrimiento y los pasos de secado so realizan en un lecho fluidizado.
. En este caso, la mezela del polvo inicial so fluidiza primero antes de ser granulada
25 pulverizando dicho polvo con la mezcla de excipientes quo comprende al menos un
aglutinante, los granos obtenidos se recubren despuØs por pulverizaciOn con la suspension
de recubrimiento, los grÆnulos recubiertos formadosse secan finalmente en el lecho
fluidizado. En al menos una realizaciOn, la mezcla de excipientes usada durante el paso
de granulaciOn y la suspensiOn de recubrimiento usada durante ci paso de recubrimiento
30 forman una inica mezcla. En este caso, el paso de granulación se puede distinguir del
paso de pulverización variando diferentes parªmetros, como la velocidad de
pulverización de la mezcla y la presión de pu!verizaciOn do dicha mezcla. Por lo tanto,
sOlo algo de la mezcla do excipientes so usa durante ci paso de granuiacion, mientras la
otra porciOn se puede usar durante el paso de recubrimiento. Por lo tanto, la velocidad do
35 pulverizaciOn do la suspensiOn do recubrimiento es mayor durante ci paso de granulaciOn
que durante ci paso de recubrimiento, mientras que la presión de pulverización de la suspension do recubrimiento es inenor durante el paso do granulación que durante el paso

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de recubrimiento. En la prÆctica,a escala de laboratorio en un dispositivo de lecho fluidizado, por ejemplo del tipo Glatt GPCG1, durante el Paso de granulación, la
velocidad de pulverización de la suspension de recubrimiento estÆ entre
aproximadamente 10 g/minuto y aproximadamente 25 g/minuto, incluidos todos los
5 valores y rangos intermedios, y la presión de pulverizaciOn estÆ entre aproximadamente 1
bar y aproximadamente 1,8 bar, incluidos todos los valores y rangos intermedios.
Durante el Paso de recubrimiento, la velocidad de pulverización de la suspension de recubrimiento estÆ entre aproximadamente 5 g/minuto y aproximadamente 15 g/minuto, incluidos todos los valores y rangos intermedios, mientras la presiOn de pulverización
10 estÆ entreaproximadamente 1,5 bar y aproximadamente 2,5 bar, incluidos todos los
valores y rangos intermedios. En al menos una realización, entre aproximadamente 10%
y aproximadamente 20%, incluidos todos los valores y rangos intermedios, de la mezela
de excipientes se pulveriza durante el paso de granulación, el resto se pulveriza durante el Paso de recubrimiento.
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Como un ejemplo profØtico de estas realizaciones que implican la granulación y el recubrimiento combinados del bromhidrato de bupropion en micropartfculas en las cuales
el fÆrmacoestÆ ubicado al menosen parte dentro del nücleo de la micropartIcula Pero
capaz de liberaciOn inmediata, las micropartIculas se pueden preparar segün el proceso
20 siguiente: Una solución de granulacion se prepara primero disolviendo aproximadamente
48 g de etilcelulosa en aproximadamente 273 g de alcohol etilico. Una suspension de recubrimiento se prepara despuØs mezelando aproximadamente 97 g de etilcelulosa, aproximadamente 28,5 g de polietilenglicol 6000, aproximadamente 26 g de
croscarmelosa de sodio, aproximadamente 10 g de sIlice precipitado y aproximadamente
25 27,5 g de aspartamo en aproximadamente 1.900 g de alcohol etIlico, hasta que se obtiene
una suspensiOn homogenea. DespuØs se fluidiza la mezcla de polvos que consiste en aproximadamente 700 g de bromhidrato de bupropion y aproximadamente 35 g de
Aedisol. DespuØs se comienza la granulaciOn pulverizando la solución de granulacion durante aproximadamente 15 a aproximadamente 20 minutos a una velocidad de
30 pulverización de aproximadamente 25 g/minuto y una presiOn de pulverizaciOn de la

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suspension de aproximadamente 0,8 bar. El recubrimiento real se realiza despuØs pulverizando la suspension de recubrimiento durante aproximadamente I hora 30
minutos a una velocidad de pulverización de aproximadamente 15 a aproximadamente 20 g/minuto y una presiOn de pulverizaciOn de la suspension de aproximadamente 1,5 bar.

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Otras realizaciones de la invención implican el recubrimiento del material de bromhidrato de bupropion, formando de ese modo una mieropartIcula que contiene fªrmaco. Uno de dichos procesos para lograr esto implica:
Mezelar y fluidizar una mezcla de polvo de principio activo y un adyuvante para obtener granos individuales,
Licuar por separado en condiciones de calor un agente de la matriz lipidica que
comprende o un ester de Æcido behØnicoy alcohol o un ester de ÆeidopalmItico/esteÆrico
y alcohol,
Recubrir la mezcla de polvos fluidizada en condiciones de calor pulverizando el agente
10 de la matriz lipIdica sobre los granos individuales,
Reducir la temperatura del producto combinado para permitir que el agente de la matriz
lipidica solidifique.

W Este proceso no requiere una fase de evaporaeión ni una fase de secado, ya que no
15 requiere un paso de granulación por via hümeda o en disolvente, haciendo posible asi que
estØ libre de todo riesgo debido a la presencia de residuos tóxicos en el producto final. AdernÆs,no es necesario Ilevar a cabo la determinaciOn cuantitativa de trazas de
disolventes, un anÆlisis quepuede ser rnuy costoso. De acuerdo con el proceso de esta realización de la invención, las condiciones de pulverización y por lo tanto las
20 caracterIsticas del recubrimiento se pueden modificar, para variar ci perfil de liberación
del bromhidrato de bupropion, variando varios parÆmetros,cuyas caracterIsticas de ajuste permanecen simples. Por lo tanto, la presión del aire de pulverización se puede aumentar
para promover la forrnación de una pelIcula hornogØnea del agente de la matriz lipidica
. airededor de los granos. De manera ventajosa, la velocidad de pulverización del agente
25 de la matriz lipidica se puede reducir sirnultÆneamente. En este caso, se obtiene ci perfil
de liberación de bromhidrato de bupropion, es decir un porcentaje de la disolución como
una función del tiempo, que puede ser bajo, correspondiente a una liberación lenta del
frmaco. Por el contrario, la presión del aire de pulverización se puede reducir para
promover la aglomeraciOn de los granos unos con otros. De manera ventajosa, la
30 velocidad de pulverizaciOn del agente de la matriz lipidica se puede aurnentar
simultÆnearnente. Eneste caso, se puede obtener un perfil de iiberación de los granos obtenidos que es alto, correspondiente a una liberación rÆpida del bromhidrato de
bupropion. En la prÆcticay de acuerdo con la masa de polvo empleada, ci valor de la velocidad de pulverización del agente de la matriz lipidica puede ser de dos a cuatro
35 veces mayor cuando se desea promover la aglorneraciOn de los granos unos con otros que
cuando se desea promover la formaeión de una pelIcula homogenea alrededor de los
granos. Por otro lado, ci valor de la presión del aire de pulverización puede ser de una a

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dos veces menor cuando se desea promover la aglomeracion de los granos unos con otros que cuando se desea promover la formación de una pelfcula homogØnea airededor de los granos. De acuerdo con el proceso para fabricar estas realizaciones, es posible, despuØs
de haber determinado m perfil de liberación del fÆrmaco dado, variar los valores de la
5 presión del aire de pulverización y de la velocidad de pulverización en toda la etapa de
recubrimiento, haciendo posible promover la formación de una peilcula homogØnea airededor de los granos o promover la aglomeración de los granos. Una vez que se ha deterniinado la secuencia de la duración de la presión del aire de pulverización y de la velocidad de pulverización, la operación de recubrimiento se puede ilevar a cabo
10 continuamente y automÆticamente. Dc acuerdocon otra caracteristica del proceso de
fabricación de estas realizaciones, la temperatura de la mezela del agente de la matriz licuado y del aire de pulverización es mayor en aproximadamente 35°C a
aproximadamente 60°C que la temperatura de fusion del agente de la matriz lipIdica. Asimismo, la temperatura del aire de fluidizaciOn y la del polvo es aproximadamente
15 igual a la temperatura de fusiOn del agente de la matriz lipIdica, mÆso menos
aproximadamente 10°C. AdemÆs,para obtener una mezela de los granos individuales, se puede usar un dispositivo de lecho fluidizado operado por aire o un dispositivo de
turbina. AdemÆs, el agentede matriz Jipidica se puede pulverizar mediante la tØcnica de pulverización de aire, es decir pulverización de lIquido a presión en presencia de aire
20 comprimido. De acuerdo con al menos una realizaciOn, se hace uso de un polvo que
comprende el fÆrmacoy el adyuvante. En otras palabras, despuØs de mezclar y fluidizar
los constituyentes combinados del polvo, el agente de la matriz lipfdica se pulveriza sobre
los granos individuales obtenidos. Para evitar la adhesion de los granos recubiertos obtenidos, ya sea en el caso en que se tratan todos los granos o ya sea en el caso en que
solo se trata una porción de los granos, se inserta una etapa de iubricación de los granos
entre la etapa de recubrimiento y la etapa de ponerlos en una forma farmacØutica. AdemÆs,para obtener mayor estabilidad de la composiciOn farmacØutica, es decir para reducir al mInimo las modificaciones en relación con la liberaciOn del bromhidrato de bupropion con el transcurso del tiempo, los grÆnuloso los comprimidos obtenidos en
30 ciertas realizaciones de este ej emplo se pueden someter a una etapa de maduración en una
estufa, durante al menos aproximadamente 8 horas, a una temperatura entre
aproximadamente 45°C y aproximadamente 60°C; y en ciertas realizaciones a aproximadamente 55°C.

35 Como un ejemplo profØtico de estas realizaciones de micropartIculas que contienen
fÆrmacoque se forman recubriendo ci material de bromhidrato de bupropion, las microparticulas que contienen fÆrmacose pueden preparar segUn ci proceso siguiente: Se

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prepara una mezcla del polvo que comprende: bromhidrato de bupropion; fosfato dicÆlcicodeshidratado; y polivinilpirrolidona. Los lotes de grÆnulos sepreparan
mediante un proceso que coruprende las etapas siguientes: se tamiza la mezcla de polvos obtenida; dicho polvo se mezcla, mientras se calienta por medio de un lecho fluidizado operado por aire, para obtener granos individuales; el agente de la matriz lipidica (behenato de glicerilo, por ejemplo COMPRITOLfi 880 ATO) se licüa por separado a aproximadamente 120°C; ci agente de la matriz lipIdica se pulveriza sobre la mezcla de polvos calentada, y, finalmente, la temperatura se reduce para permitir que ci agente de la matriz lipIdica solidifique. Estas etapas se lievan a cabo mientras se varian diversos parÆmetros,ya sea para promover la formación de una pelicula homogØnea alrcdedor de los granos o para promover la aglomeración de los granos, de conformidad con la tabla siguiente:

ParÆmetros Lote 1 Lote 2 Lote 3 Lote 4

en peso de la matriz lipIdica
Agente (COMPRITOLfi 888 ATO) 5 4 4 5
Velocidad deflujode aire de
fluidización (m3/h)

80 110 80 80

Aglomeración
Presión del aire de pulverización (bar) 2 1,5 1,5
Temperatura del lecho de polvo (°C) 70 70 74
Velocidad de pulverización para
COMPRITOLfi (g/min)

42 40 40

Recubrimiento

Presión del aire de pulverización (bar) 2,5 3,5 2 2
Temperatura del lecho de polvo (°C) 70 66 71 70
Velocidad de pulverización para
COMPRITOLfi (g/min)

41 20 40 40

Otra realización de la invención para recubrir ci material de bromhidrato de bupropion, formando de ese modo una micropartleula que contiene fÆrmaco,implica la formación de microcristales recubiertos que se pueden incorporar posteriormente en un comprimido. Mediante selecciOn del polImero apropiado los microcristales pueden poseer caracteristicas diversificadas como resistencia gÆstricay liberación controlada debido al hecho de que dichos microcristales y microgrÆnulosrecubiertos o sin recubrir conserven, despuØs de que se les haya dado forma de un comprimido multiparticulado, sus propiedades iniciales entre las cuales estªn incluidos ci enmascararniento del sabor, la

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resistencia gÆstricay la liberación controlada del brombidrato de bupropion. En ciertas realizaciones de este ejemplo, la lista no limitante de polImeros siguiente se puede seleccionar para el recubrimiento del bromhidrato de bupropion en el equipo de recubrimiento convencional basado en la fluidización: etilcelulosa (EC);
5 hidroxipropilcelulosa (HPC); hidroxipropilinetilcelulosa (HPMC); gelatina;
gelatina/acacia; gelatina!acacia/Øter vinilmetIlico-anhidrido maleico; gelatinalacacialanhIdrido etilenmaleico; carboximetilcelulosa; alcohol polivinIlico;
acetato ftalato de celulosa; nitrocelulosa; laca; cera; polimeros de polimetacrilato como EUDRAGITfi RS; EUDRAGITfi RLo coinbinaciones de ambos, EUDRAGITfi E y
10 EUDRAGIT NE30D; KOLLICOATTM SR3OD; y sus rnezclas.

MicropartIculas distribuidas en capas de fÆnnaco
Las microparticulas distribuidas en capas de fÆrmacode ciertas realizaciones se pueden preparar recubriendo una particula inerte o ntc1eo, como una esfera nonpareil (por
15 ejemplo, una esfera de azücar), con la sal bromhidrato de bupropion y un aglutinante
polimØrico. En ciertas realizaciones de las micropartfculas distribuidas en capas de fÆrmaco,los nücleos inertes incluyen materiales insolubles en agua como las esferas de celulosa o dióxido de silicio. En otras realizaciones, los næcleos inertesincluyen
materiales solubles en agua como esferas de almidón, sal o azücar. Los nücleos inertes
20 pueden tener un diÆmetro quevarla entre aproximadamente 100 micras y
aproximadamente 2.000 micras, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el diÆmetro de los nücleos inertes varia entre aproximadamente 150 micras y aproximadamente 1.500 micras. En al menos una
realización, los nücleos inertes son esferas de azUcar NF, que contienen no menos de
025 aproximadamente 62,5% y no mÆsde aproximadamente 91,5% de sacarosa, incluidos
todos los valores y rangos interniedios. En al menos una realización los nücleos inertes
tienen densidad aparente sustancialmente uniforme, friabilidad baja y propiedades de
generación de polvo bajas. En al menos una realización, los nUcleos inertes se recubren
con un sub recubrimiento osmOtico que comprende un agente osmótico y un aglutinante
30 polimØrico. AdemÆs, losnücleos inertes se pueden recubrir inicialmente con un
recubrimiento sellador para proporcionar una superficie del nücleo mÆs uniformey para reducir al minimo cualquier efecto osmótico. La capa de recubrimiento sellador se puede aplicar al nic1eo antes de la aplicación del fÆrmaco, el aglutinante polimØrico y todas las capas de pelIcula polimØrica. En al menos una realización, la capa de recubrimiento
35 sellador no modifica sustancialmente la liberación de la sal bromhidrato de bupropion.
Los ejemplos de los materiales selladores adecuados que se pueden usar en el
recubrimiento sellador incluyen agentes permeables o solubles como

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hidroxipropilmetilcelulosa, hidroxipropilcelulosa, etilcelulosa, un poilmero
polimetacrilato, hidroxipropiletilcelulosa, goma xantano y sus mezclas. En al menos una realizaciOn el sellador usado en el recubrimiento sellador es hidroxipropilmetilcelulosa.
Se pueden agregar otros agentes para mejorar la procesabilidad del sellador. Los
5 ejemplos de dichos agentes incluyen talco, silice coloidal, alcohol polivinIlico, dióxido de
titanio, silice micronizado, silice ahumado, monoestearato de glicerol, trisilicato de magnesio, estearato de magnesio y sus mezclas. La capa de recubrimiento sellador se
puede aplicar a partir de una solución (por ejemplo, acuosa) o suspensiOn usando un
revestidor de leeho flüidizado (por ejemplo, recubrimiento de Wurster), o en un sistema
10 de recubrimiento de paila. Los ej emplos de dichos recubrimientos selladores estÆn
comercialmente disponibles (por ejemplo, OPADRYfi Blanco Y-1-7000 y OPADRYfi
Blanco OY/B/28920).

10 El aglutinante de estas realizaciones distribuidas en capas de fÆrmaco se usa paraadherir
15 la capa de sal bromhidrato de bupropion al rn’ieleo inerte o recubrimiento sellador del
nÆcleo. En ciertas realizaciones, el aglutinante es soluble en agua, posee una adhesividad suficientemente alta para adherir la capa de sal bromhidrato de bupropion al nücleo inerte
y posee una viscosidad apropiada para proporcionar una adhesiOn importante entre ci
nücleo inerte y la sal bromhidrato de bupropion. En otras realizaciones el aglutinante es
20 insoluble en agua. En al menos una realización ci aglutinante es etilcelulosa, un polImero
de polimetacrilato, alcohol polivinflico, polivinilpirrolidona, copolimero de polivinilpirrolidona-acetato de vinilo (como KOLLIDONfi YAM), hidroxietilcelulosa, hidroxipropilmetilcelulosa de bajo peso molecular (por ejemplo, viscosidad de aproximadamente 1-50 cp a aproximadamente 20°C; aproximadamente 2-12 cp a
25 aproximadamente 20°C;o aproximadamente 4-6 cp a aproximadamente 20°C),
polimetacrilatos de hidroxipropilcelulosa o sus mezclas. Por ejemplo, en ciertas realizaciones la composición del aglutinante para ci bromhidrato de bupropion es de aproximadamente 1% a aproximadamente 25% p/p, incluidos todos los valores y rangos intermedios; en otras realizaciones de aproximadamente 2% a aproximadamente 10%
30 pIp; y aun en otras realizaciones de aproximadamente 3% a aproximadamente 5% pIp,
expresada como un poreentaje del peso total del nücleo.

Se pueden usar disolventes para aplicar la sal bromhidrato de bupropion al nücleo inerte, cuyos ejempios incluyen aicoholes inferiores como etanol, isopropanol y mezclas de
35 alcohol/agua, acetona e hidrocarburos ciorados.

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Las micropartIculas distribuidas en capas de fÆrmacose pueden preparar formando una suspension o soh.ición del aglutinante y la sal brornhidrato de bupropion y despuØs distribuyendo en capas la suspensiOn o solución sobre el nÆcleo inerte o nücleo subreeubierto usando cualquiera de las tØcnicas de distribuciOn en capas conocidas en el
area, como recubrimiento en lecho fluidizado o recubrimiento en paila. Esto se puede efectuar en un ünico recubrimiento o ci proceso se puede lievar a cabo en multiples
capas, opcionalmente con pasos intervinientes de secado/evaporaciOn. Este proceso se
puede conducir de modo de producir micropartleulas que contienen una eantidad deseada
de sal bromhidrato de bupropion y lograr la dosificaciOn y liberación deseadas con la

10 administraciOn in vivo.

En ciertas realizaciones, las micropartIculas distribuidas en capas de fÆrmaco se pueden preparar usando por ejemplo, ci procedimiento del experimento hipotØtico siguiente: Se disuelven bromhidrato de bupropion (aproximadamente 2,8 kg) e
15 hidroxipropilmetilcelulosa (METHOCELfi ES) (aproximadamente 0,40 kg) en una
mezcla de agua y alcohol isopropIlico. DespuØs la soluciOn de fÆrmacoactivo se puede pulverizar sobre las esferas de azücar 30/35 (aproximadamente 1,06 kg) en un procesador
de lecho fluidizado con un separador de Wurster. DespuØs las micropartleulas del nücleo
activo se pueden secar en un procesador de lecho fluidizado hasta que la pØrdida por
20 secado estÆ por debajo de 1% aproximadamente. Las micropartIculas de bupropion se
pueden pasar despuØs a travØs de un tamiz de malla 16 y un tamiz de malla 30 y se
pueden recoger micropartIculas mÆspequeæas que una malla 16 y mÆs grandesque una
malla 30.

025 Recubrimientos que enmascaran ci sabor de las micropartleulas
Cada una de las micropartIcuias de la presente invenciOn se puede recubrir con al menos
un recubrimiento que enmascara ci sabor. El recubrimiento que enmascara el sabor
puede enmascarar el sabor del fÆrmacoactivo en las micropartleulas. En al menos una realización las formulaciones de recubrimiento que enmascara ci sabor contienen
30 ingredientes polimØricos. Se contempla que se pueden usar en el recubrimiento otros
excipientes compatibles con los objetivos de la presente invención que enmascaran ci
sabor.

En al menos una realizaciOn, el recubrimiento que enmascara ci sabor comprende un
35 polImero como la etilcelulosa, que se puede usar como un poilmero seco (como
ETHOCELfi) solubilizado en un disolvente orgÆnico antesde usar, o como una
dispersion acuosa. Una dispersiOn acuosa comercialmente disponible de etilcelulosa es

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AQUACOATfi. El AQUACOATfi se puede preparar disolviendo la etilcelulosa en un disolvente orgÆnico inmiscibie conagua y luego emuisionar el mismo en agua en
presencia de un tensioactivo y un estÆbilizador. DespuØs de la hornogeneizaciOn para generar gotitas submicrónicas, ci disolvente orgÆnicoSe evapora al vaclo para formar un
5 pseudolÆtex. El plastificante no se incorpora en ci pseudolÆtex durantela fase de
fabricación. Por lo tanto, antes de usar el mismo como un recubrimiento, el
AQUACOATfi se rnezcla bien con un plastificante adecuado antes de usar. Otra dispersion acuosa de etilcelulosa se comercializa como SURELEASEfi. Este producto
se puede preparar incorporando un plastificante en la dispersion durante el proceso de
10 fabricación. Se prepara una masa fundida caliente de un poilmero, un plastificante (por
ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, Æcido oleico)como una mezcla homogØnea, que luego se diluye con una solución alcalina para obtener una dispersion acuosa que Se puede aplicar directarnente sobre los sustratos.

15 En otras realizaciones, se pueden emplear poilmeros acrilicos de polirnetacrilato como
polimeros que enmascaran el sabor. En al menos una realizaciOn, el recubrimiento que enmascara el sabor es una laca de resina acrIlica usada en forma de una dispersion acuosa (por ejemplo, EUDRAGITfi o KOLLICOATfi). En otras realizaciones, el recubrimiento acrflico comprende una mezela de dos lacas de resina acrflicas (por ejemplo,
20 EUDRAGITfi RL y EUDRAGITfi RS, respectivamente).

EUDRAGITfi RL y EUDRAGITfi RS son copolIrneros de Østeres acrilicos y
metacrilicos con un contenido bajo de grupos amonio cuaternario, la reiación molar entre

10 los grupos amonio y los restantes Østeres (met)acrilicos neutros es de 1:20 en
25 EUDRAGITfi RL y 1:40 en EUDRAGITfi RS. El peso molecular medio es 150.000.
Las designaciones del código RL (permeabilidad alta) y RS (penneabilidad baja) se
refieren a las propiedades de penneabilidad de estos agentes. Las mezclas EUDRAGITfi RL/RS son insolubles en agua y en los lfquidos digestivos. Sin embargo, los
recubrimientos elaborados a partir de ellos son hinchables y penneables en soluciones
30 acuosas y lIquidos digestivos. Las dispersiones o soluciones de EUDRAGITfi RL/RS de
ciertas realizaciones se pueden mezclar en cualquier proporción deseada para obtener en iiltimo tØrmino un recubrimiento que enmascara ci sabor con un perfil deseable de disoluciOn del fÆrmaco. Enciertas realizaciones, se pueden obtener formulaciones, por ejemplo, a partir de tin recubrimiento derivado de 100% de EUDRAGITfi RL; 50% de
35 EUDRAGITfi RL con 50% de EUDRAGITfi RS; y 10% de EUDRAGITfi RL con 90%

de EUDRAGITfi RS

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En otras realizaciones, el poilmero que enmascara el sabor puede ser un polimero acrIlico
de carÆcter catiónico a base de metacrilato de dimetilaminoetilo y Østeres del Æcido metacrIlico neutros (por ejemplo, EUDRAGITfi E). Los recubrimientos de poilmero
acrilico hidrófobo de la presente inveneión pueden incluir ademÆs un copolimero neutro a
5 base de poli(met)acrilatos, como EUDRAGITfi NE. Las peliculas de laca de
EUDRAGITfi NE 30D son insolubles en agua y liquidos digestivos, pero permeables e hinchables.

En otras realizaciones, ci polImero que enmascara el sabor es una dispersion de
10 poli(acrilato de etilo, metacrilato de metilo) 2:1 (KOLLICOATfi EMM 30 D, BASF).

En otras realizaciones, el poilmero que enmascara el sabor puede ser un acetato polivinflico estabilizado con polivinilpirrolidona y lauril sulfato de sodio como KOLLICOATfi SR30D
15

Otros polimeros que enmascaran el sabor incluyen hidroxipropilcelulosa (HPC); hidroxipropilmetilcelulosa (HPMC); hidroxietilcelulosa; gelatina; gelatina/acacia; gelatina’acacialØter vinil metulico-anhidrido maleico; gelatinalacacialanhidrido
etilenmaleico; carboximetilcelulosa; alcohol polivinIlico; nitrocelulosa; copoilmeros
20 injertados de alcohol polivinIlico-polietilenglicol; laca; cera y sus mezelas.

Los recubrimientos que enmascaran el sabor se pueden aplicar a las micropartfculas a
partir de una o mÆssoluciones o suspensiones de disolventes orgÆnicos o acuosos. En at
menos una realización los disolventes orgÆnicosque se pueden usar para aplicar los
025 recubrimientos que enmascaran el sabor incluyen uno o mÆs entre acetona, aicoholes
inferiores como etanol, isopropanol y mezclas aicohol/agua, hidrocarburos elorados y
similares. Los dispositivos empleados para recubrir las micropartIculas de la invención
con un recubrimiento que enmascara el sabor incluyen los convencionalmente usados en
el procesamiento farmacØutico, como los dispositivos de recubrimiento de lecho
30 fluidizado, Los recubrimientos aplicados a las micropartIculas pueden contener
ingredientes diferentes de los poilmeros funcionales. TarnbiØn se pueden usar uno o mÆs colorantes, aromatizantes y edulcorantes en el recubrimiento que enmascara el sabor.

En algunas realizaciones se puede incluir un formador de poros en el recubrimiento que
35 emnascara el sabor para influir en la velocidad de liberaciOn del bromhidrato de
bupropion desde la micropartIcula. En otras realizaciones, no se inciuye un forinador de poros en el recubrimiento que enmascara el sabor. Los formadores de poros pueden ser

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inorgÆnicosu orgªnicos e incluyen materiales como los materiales particulados que se pueden disolver, extraer o lixiviar del recubrimiento en el ambiente de uso. DespuØs de
la exposición a liquidos en el ambiente de uso, los formadores de poros se pueden, por ejemplo, disolver y Se forman canales y poros que se ilenan eon el lIquido ambiental.

5

Por ejemplo, los formadores de poros de ciertas realizaciones pueden comprender uno o mÆspolirneros hidrOfilos solubles en agua para modificar las caracteristicas de liberación
de la formulación. Los ejemplos de los polfmeros hidrófilos adecuados usados como formadores de poros incluyen hidroxipropilmetileelulosa, Øteres de celulosa y derivados
10 proteicos de estos polimeros, los Øteres de celulosa, como hidroxialquilcelulosas y
carboxialquilcelulosas. AdernÆs,se pueden usar polImeros solubles en agua sintØticos, cuyos ejemplos incluyen polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de polietileno, polidextrosa soluble en agua, sacÆridosy polisacÆridos, como pullulan, dextrano, sacarosa, glucosa, fruetosa, manitol, lactosa, manosa, galactosa, sorbitol y sus
15 mezclas. En al menos una realizaciOn, el polirnero hidrófilo comprende
hidroxipropilmetilcelulosa.

Otros ejemplos no limitantes de formadores de poros que se pueden usar en ciertas realizaciones que contengan un recubrimiento que enmascara el sabor incluyen sales de
20 metales alcalinos como carbonato de litio, cloruro de sodio, bromuro de sodio, cloruro de
potasio, sulfato de potasio, fosfato de potasio, acetato de sodio, citrato de sodio y sus
mezclas. Los sOlidos formadores de poros tambiØn pueden ser polIrneros solubles en el ambiente de uso, como los CARBOWAXTM y CARBOPOLTM. AdernÆs, losformadores
. de poros abarcan dioles, polioles, alcoholes polihIdricos, polialquilenglicoles,
25 poliglicoles, poli(a-w)alquilendioles y sus mezclas. Otros formadores de poros que
pueden ser i’itiles en las formulaciones de ciertas realizaciones de la presente invención incluyen almidón, alrnidón modificado y derivados del almidón, gornas, incluidas, pero
no exelusivarnente, goma xantano, ÆcidoalgInico, otros alginatos, bentonita, veegum
(silicato de alurninio y magnesio), agar, goma guar, goma de algarrobo, goma arÆbiga,
30 quince psyllium, semilla de lino, goma de quimbombO, arabinogalactano, pectina, goma
tragacanto, escieroglucano, dextrano, amilosa, amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de intercambio iónico, corno polirnetacrilato de potasio, carragenina, carragenina kappa, carragenina lambda, goma karaya, goma biosintØtica, y sus mezclas. Otros formadores de poros incluyen materiales Uæles para
35 hacer lÆrninasmicroporosas en los ambientes de uso, como policarbonatos compuestos de
poliØsteres lineales del Æcido carbOnico en los quelos grupos carbonato reaparecen en la eadena polimØrica, materiales microporosos como bisfenol, un poli(cloruro de vinilo)

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microporoso, poliamidas microporosas, copoilmeros modacrilicos microporosos, estireno-acrilico microporoso y sus copoilmeros, polisulfonas porosas, poli(vinilideno) halogenado, policloroØteres, poilnieros de acetal, poliØsteres preparados por esterificación
de un Æcido dicarboxulico oanhidrido con un aiquilenpoliol, poli(sulfuros de aiquileno),
5 fenólicos, poliØsteres, polimeros porosos asimØtricos, pollmeros olefinicos reticulados,
homopoilmeros hidrófilos microporosos, copolImeros o interpolimeros con una menor densidad aparente y otros materiales similares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas), poli(benzimidazoles), colodión, protelnas regeneradas, poli(vinilpirrolidona) reticulada semisólida y sus mezclas.

10

En general, la cantidad de formador de poros incluida en los recubrirnientos que
enmascaran el sabor de ciertas realizaciones de la presente invención pueden ser de aproximadamente 0,1% a aproximadamente 80%, en peso, incluidos todos los valores y rangos intermedios, en relación con el peso combinado de polimero y formador de poros.
15 Como el porcentaje de formador de poros se relaciona con el peso seco del polimero que
enmascara el sabor, puede tener una influencia en las propiedades de liberación del
farmaco desde la microparticula recubierta. En al menos una realización que usa
formadores de poros solubles en agua como hidroxipropilmetilcelulosa, puede haber presente una relación de pesos secos de polimero que enmascara el sabor:formador de
20 poros de aproximadamente 10:1 a aproximadamente 1:1, incluidos todos los valores y
tangos intermedios. En ciertas realizaciones la relación de pesos secos de polimero que enmascara el sabor:formador de poros es de aproximadamente 8:1 a aproximadamente
1,5:1; y en otras realizaciones de aproximadamente 6:1 a aproximadamente 2:1. En al
menos una realizaciOn que usa EUDRAGITfi NE30D como polimero que enmascara el
025 sabor y una hidroxipropilmetilcelulosa (viscosidad aprox. 5 cp (en una solución acuosa al
2%)) como METHOCELfi ES, Pharmacoat 606G como el formador de poros soluble en
agua, estÆpresente una relación de pesos secos polimero que enmascara el
sabor:formador de poros de aproximadamente 2:1.

30 Los colorantes que se pueden usar en el recubrimiento que enmascara el sabor incluyen
los colorantes de alimentos, fÆrmacosy cosmØticos (FD&C), de fÆrmacosy cosmØticos
(D&C), o los colorantes externos (Ext. D&C). Estos colorantes son tinturas, lacas y
ciertos colorantes naturales y derivados. Las lacas ütiles incluyen tinturas absorbidas
sobre hidróxido de aluminio u otros soportes adecuados.
35

Los saborizantes que se pueden usar en el recubrimiento que enmascara el sabor incluyen liquidos saborizantes naturales y sintØticos. Una lista ilustrativa de dichos saborizantes

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incluye aceites volÆtiles,aceites saborizantes sintØticos, compuestos aromÆticos saborizantes, aceites, lIquidos, oleorresinas y extractos derivados de plantas, hojas, fibres, frutos, tallos y sus combjnacjones. Una lista representativa, no limitante, de Østos incluye aceites eltricos, como de limón, naranja, toronja, Jima y pomelo y esencias de frutas,
incluidas manzana, pera, durazno, uva, frutilla, frambuesa, cereza, ciruela, ananÆs, albaricoque u otros saborizantes de fruta. Otros saborizantes Utiles incluyen aldehIdos y Østeres, como benzaldehfdo (cereza, almendra); citral, es decir, alfa citral (limOn, lima);
neral, es decir, beta citral (limón, Jima); decanal (naranja, limon); aldehIdo C-8 (cItricos); aldehIdo C-9 (eftrjcos); aldehIdo C-12 (citricos); tolil aldehIdo (cereza, almendra); 2,6-
10 dimetiloctanal (fruto verde); 2-dodenal (mandarina); y sus mezclas.

Los edulcorantes que se pueden usar en el recubrimiento que enmascara el sabor incluyen glucosa (jarabe de mafz), dextrosa, azücar invertido, fructosa y sus mezclas (cuando no se usa como un vehIculo); sacarina y sus diversas sales, como la sal de sodio; dipØptidos.
15 edulcorantes como el aspartamo; compuestos dihidrochalcona, glicirricina; Steva
Rebaudiana (esteviósido); derivados clorados de sacarosa como sucralosa; y alcoholes de azücares como sorbitol, manitol, xilitol y similares. TambiØn estÆncontemplados los hidrolizados de almidón hidrogenados y los edulcorantes sintØticos como 3,6-dihidro-6-metil-1-1-1,2,3-oxatiazin-4-1-2,2-di6xido, en particular la sal de potasio (acesulfamo-K)
20 y sus sales de sodio y calcio. Los edulcorantes se pueden usar solos o en cualquier
combinación.

El recubrimiento que enmascara el sabor de la microparticula tambiØn puede incluir uno
o mÆsexcipientes farmacØuticamente aceptables como lubricantes, emulsionantes,
 25 antiespumantes, plastificantes, disolventes y sirnilares.

Se pueden incluir lubricantes para ayudar a reducir la fricción de las micropartIculas
recubiertas durante la fabricación. Los lubricantes que se pueden usar en el
recubrimiento que enmascara el sabor de la presente invención incluyen, pero no
30 exclusivamente, Æcidoadipico, estearato de magnesio, estearato de calcio, estearato de
cinc, silicato de calcio, silicato de magnesio, aceites vegetales hidrogenados, cloruro de
sodio, esterotex, polioxietileno, monoestearato de glicerilo, talco, polietilenglicol,
benzoato de sodio, lauril sulfato de sodio, lauril sulfato de magnesio, estearil furnarato de sodio, aceite mineral ligero, Østeres de Æcidosgrasos como bebenato de glicerilo, (es decir
35 COMPRITOLTM), STEAR-O-WETTM, MYVATEX TMTL y sus rnezclas. En al menos
una realización, el lubricante Se selecciona entre estearato de magnesio, talco y una
mezcla de los mismos. Las combinaciones de estos lubricantes son factibles. Cada

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lubricante puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 100% en peso del peso seco del polimero en el recubrimiento que enmascara el sabor, incluidos todos los valores y rangos intermedios. Pot ejemplo, en ciertas realizaciones en las que el poilmero que enmascara el sabor es EUDRAGITfi
5 NE30D o EUDRAGITfi NE40D junto con un formador de poros hidrófflo, el lubricante
estª presente en una cantidad entre aproximadamente 1% y aproximadamente 30% en
peso del peso seco del polimero; en otras realizaciones entre aproximadamente 2% y aproximadamente 20%; y aun en otras realizaciones en aproximadamente 10% en peso
del peso seco del recubrimiento que enmascara el sabor de la microparticula. En otra
10 realización en la que el polimero que enmascara el sabor es etilcelulosa (ETHOCELTM
poilmero PR100, PR45, PR20, PR10 o PR7, o una mezcla), el lubricante puede estar presente en una cantidad entre aproximadamente 10% y aproximadamente 100% en peso
del peso seco del recubrimiento que enmascara el sabor de la microparticula; en otra realización entre aproximadamente 20% y aproximadamente 80%; y aun en otras
15 realizaciones en aproximadamente 50% en peso del peso seco del recubrimiento que
enmascara el sabor de la microparticula. En otras realizaciones, el recubrimiento que enmascara el sabor no incluye un formador de poros.

Se pueden incluir uno o mÆsemulsionantes (tambiØn denominados emulsionantes o
20 emulgentes) en el recubrimiento que enmascara ci sabor de la microparticula para
facilitar la emulsificación real durante la fabricación del recubrimiento y tambiØn para asegurar la estabilidad de la emulsion durante la vida ütil en depOsito del producto. Los emulsionantes ütiies para el recubrimiento que enmascara el sabor de la micropartIcula de ciertas realizaciones incluyen, pero no exelusivamente, materiales de origen natural y sus derivados semisintØticos, como los polisacÆridos, asI como Østeresde glicerol, Øteres de celulosa, Østeres de sorbitªn (por ejemplo, monooleato de sorbitÆn oSPANTM 80) y polisorbatos (por ejemplo, TWEENTM 80). Las combinaciones de emulsionantes son factibles. En al menos una realizaciOn, el emulsionante es TWEENTM 80. El o los emulsionante(s) pueden. estar presentes en una cantidad entre aproximadamente 0,01% y
30 aproximadamente 5% en peso del peso seco del polimero que enmascara el sabor de la
microparticula, incluidos todos los valores y rangos intermedios. Pot ejemplo, en ciertas realizaciones ci emulsionante estÆ presenteen una cantidad entre aproximadamente
0,05% y aproximadamente 3%; en otras realizaciones entre aproximadamente 0,08% y aproximadarnente 1,5%, y aun en otras realizaciones en aproximadamente 0,1% en peso
35 del peso seco del polimero que enmascara el sabor de la microparticula.

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Se pueden incluir uno o mÆsantiespumantes en el recubrimiento que enmascara el sabor
de la microparticula para reducir la producción de burbujas o de espuma durante la fabricación del recubrimiento. Los antiespumantes ütiles para la eoxnposición del recubrimiento incluyen, pero no exciusivamente, simeticona, poliglicol, aceite de siiicio y
5 sus mezclas. En al menos una reaiización, el antiesputnante es simeticona C. El
antiespurnante puede estar presente en una cantidad entre aproximadamente 0,1% y aproximadamente 10% del peso del recubrimiento que enmascara el sabor de la microparticula, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el antiespumante estÆ presente en unacantidad entre aproximadamente
10 0,2% y aproximadamente 5%; en otras realizaciones entre aproximadamente 0,3% y
aproximadamente y aun en otras realizaciones en aproximadamente 0,6% en peso del peso seco del polIrnero que enmascara el sabor de la microparticula.

Se pueden incluir uno o mÆspiastificantes en el recubrimiento que enmascara ci sabor de
15 la microparticula para proporcionar mayor flexibilidad y durabilidad durante la
fabricación. Los plastificantes que se pueden usar en ci recubrimiento que enmascara ci sabor de la microparticula de ciertas realizaciones inciuyen monoglicØridos acetilados;
acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo;
ftalato de dimetilo; etil fialil etil glicolato; glicerina; propilenglicol; triacetina;
20 tripropioina; diacetina; ftalato de dibutilo; monoglicØrido de acetilo; acetil trietil citrato,
polietilenglicoles; aceite de ricino; aceite de coiza, aceite de oliva, aceite de sØsamo,
citrato de trietilo; alcoholes polihIdricos, glicerol, glicerina, sorbitol, Østeres de acetato, triacetato de glicerol, acetil trietil citrato, ftalato de dibencilo, ftalato de dihexilo, octil ftalato de butilo, ftalato de di isononilo, octil ftalato de butilo, azelato de dioctilo, talato
25 epoxidado, trirnelitato de triisoctilo, ftalato de dietiihexilo, ftalato de di-n-octiio, ftalato
de di-i-octilo, ftalato de di-i-decilo, ftalato de di-n-undecilo, ftalato de di-n-tridecilo, trimelitato de tri-2-etilhexiio, adipato de di-2-etilhexilo, sebacato de di-2-etilhexilo,
azelato de di-2-etiihexilo, sebacato de dibutilo, oxalato de dietilo, malato de dietilo, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo,
30 sebacato de dibutilo, tributirato de glicerol y sus mezclas. El plastificante puede estar
presente en una cantidad entre aproximadamente 1% y aproximadamente 80% del peso seco del polirnero que enmascara ci sabor, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci plastificante estÆ presente enuna cantidad entre aproximadamente 5% y aproximadamente 50%, en otras realizaciones
35 entre aproximadamente 10% y aproximadamente 40% y aun en otras realizaciones en
aproximadamente 20% del peso seco del poilmero que enmascara ci sabor,

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El recubrimiento que enmascara el sabor puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 90% en peso de la microparticula, incluidos todos los valores y rangos intermedios, dependiendo de la elecciOn del polimero, la
relación polImero:formador de poros y el area superficial total de la formulaeión de la
5 micropartIcula. Puesto que tiene que lograrse un cierto espesor del recubrimiento que
enmascara el sabor para lograr un enmascaramiento eficaz del sabor, la cantidad de recubrimiento de polimero que enmascara el sabor usada durante la fabricación estÆ relacionada con el area superficial total del lote de microparticulas sin recubrir que
requiere un recubrimiento. La cobertura del area superficial del polimero que enmascara
10 el sabor puede variar de aproximadamente 0,5 mg/cm2 a aproximadamente 20 mg/cm2,
incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones la cobertura del area superficial del polimero que enmascara el sabor es de
aproximadamente 0,6 mg/cm2 a aproximadamente 10 mg/cm2, y en otras realizaciones es
de aproximadamente 1 mg/cm2 a aproximadamente 5 mg/cm2. En al menos una
15 realización de la invención, se emplea EUDRAGITfi E como el polImero que enmascara
el sabor a una cobertura de area superficial de 4 mg/cm2. Un enfoque para estimar el area superficial total de un Tote multiparticulado es el mØtodo de permeabilidad segün Blame (ASTM Des. C 205-55), que Se basa en el modelo matemÆtico de fiujo laminar atravØs
de capilares dispuestos en paralelo.
20

A falta de una determinación exacta del area superficial total de una micropartIcula, la cantidad de polimero que enmascara el sabor que se debe aplicar Se puede expresar como
un porcentaje de la micropartIcula sin recubrir. Por ejemplo, en ciertas realizaciones el recubrimiento que enmascara el sabor estÆ presenteen una cantidad entre
5 aproximadamente 5% y aproximadamente 60%, incluidos todos los valores y rangos
intermedios; en otras realizaciones entre aproximadamente 10% y aproximadamente
40%; y aun en otras realizaciones entre aproximadamente 15% y aproximadamente 35%
en peso de la micropartIcula. En al menos una rea.lización, el recubrimiento que
eninascara el sabor estÆ presente en una cantidad deaproximadamente 30% en peso de la
30 micropartIcula.

En ciertas realizaciones, el diametro de las microparticulas (con o sin recubrimiento que enmascara el sabor) varla de aproximadamente 50 m a aproximadamente 800 tm,
incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el
35 diÆmetrode las micropartIculas varia de aproximadamente 100 pm a aproximadamente
600 tm y en otras realizaciones de aproximadamente 150 tm a aproximadamente 450

tm.

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Recubrirniento de liberación controlada de la microparticula
Cada una de las microparticulas de la presente invención Se puede recubrir con al menos
un recubrimiento de liberación controlada. Como se usa aqul, la expresión
5 "recubrimiento de liberación controlada de la microparticula" hace referencia at
recubrimiento de liberación controlada que prÆcticarnente rodea cadamicroparticula. El recubrimiento de liberación controlada de la micropartIcula se diseia para lograr una liberación controlada de la sal bromhidrato de bupropion desde la microparticula. Por ejemplo, el recubrimiento de liberación controlada de la microparticula puede ser un
10 recubrimiento entØrico con baja solubilidad a un pH gÆstricopara reducir o minimizar la
liberación del fÆrmaco en la luz del estómago, al tiempo que posee una solubilidad dependiente del pH para facilitar la liberación del fÆrmaco en el duodeno. En otra realización, el recubrimiento de liberación controlada puede ser un recubrimiento de liberaciOn retardada que proporciona una liberación retardada de la sal brornhidrato de
15 bupropion con un tiempo de retraso predeterminado que es independiente del pH del
medio de disoluciOn o aiternativarn.ente dependiente de dicho pH del medio de
disolución. Por ejemplo, aumentando el espesor del recubrimiento de liberación
controlada de la microparticula usando un poilmero de difusiOn independiente del pH se pueden lograr tiempos de retraso de aproximadamente 1 hora, aproximadamente 2 horas,
20 aproximadamente 3 horas, aproximadamente 4 horas, aproximadamente 5 horas,
aproximadamente 6 horas, aproximadamente 7 horas, aproximadamente 8 horas, aproximadamente 9 horas, aproximadamente 10 horas, aproximadamente 11 horas o aproximadamente 12 horas. Alternativamente, se pueden seleccionar polImeros de
liberación controlada que se tornan solubles por encima de un determinado pH, La
25 liberación del fªrmaco desde un sistema como ese se reduce o minirniza basta que Se
excede el pH determinado para el polImero de elección. Con cualquiera de los enfoques,
a continuación del retraso predeterminado, el fÆrrnacose libera, por ejemplo en el
transcurso de aproximadamente 1 hora para un impulso de liberaciOn i.nmediata, o alternativaniente durante un periodo prolongado, por ejemplo de aproximadamente 3 a
30 aproximadamente 24 horas. En otras realizaciones, el recubrimiento de liberación
controlada de la microparticula puede proporcionar una barrera de difusión que es independiente del pH, facilitando asf un perfil de liberación sostenida, produciØndose una liberación prÆcticatnentetotal de la sal brornhidrato de bupropion entre aproximadamente
3 y aproximadamente 24 horas despuØs de la administración. En al menos una
35 reaiizaciOn, el recubrimiento de liberación controlada de la microparticula proporciona
una liberación retardada y sostenida de la sal brornhidrato de bupropion desde la

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micropartfeula con una liberación prªcticamente total en aproximadamente las 24 horas siguientes a la administración.

En ciertas realizaciones, el recubrimiento de liberación controlada de la microparticula
puede proporcionar una liberación prÆcticamente total de la sal bromhidrato de bupropion desde la micropartIcula sin requerir ci uso de ningün formador de poros. Los formadores
de poros innecesarios que no son requeridos en el recubrimiento de iiberaciOn controlada
de la micropartleula incluyen poilmeros hidrófilos como hidroxipropilmetilcelulosa.

10 El recubrimiento de liberaciOn controlada de la micropartIcula incluye al menos un
poilmero en una canticlad suficiente Para lograr una liberación controlada de la sal bromhidrato de bupropion. En al menos una realización de la invención el polimero de liberación controlada es un polImero acrflico. Los polimeros acrilicos adecuados
incluyen, Pero no exclusivamente, copolImeros del Æcido acrilicoy ci Æcido metacrilico,
15 copolfmeros de metacrilato de metilo, metacrilatos de etoxietilo, metacrilato de
cianoetilo, copoiImero de metacrilato de aminoalquilo, poli(ÆcidoacrIlico), poli(Æcido metacrIlico), copoilmero de Æcido metacrulico aiquilamina,poli(metacrilato de metilo), poli(acido metacrulico) (anhIdrido), copoilmeros de metacrilato de glicidilo y sus
mezclas.
20

En al menos una realización, ci recubrimiento de liberación controlada coruprende
compuestos de amonio cuaternario polimerizables, cuyos ej emplos no limitantes incluyen
Østeres aminoalquulicosy aminoalquilamidas cuaternizados del Æcido acrIlicoy ci Æcido metacrIiico, por ej empio metosulfato de f3-metacril-oxietil-trimetil-amonio, cloruro de 0-
 25 acriloxi-propil-trimetil-amonio, metosulfato de trimetilaminometil-metacrilamida y sus
mezclas. El Ætomo de amonio cuaternario tambiØnpuede formar parte de un heterociclo,
como en ci cloruro de metacriloxietilmeti!-morfolinio o la correspondiente sal de
piperidinio, o se puede unir a un grupo Æcido acrulico oa un grupo ªcido rnetacrIlico a
travØs de un grupo que contiene heteroÆtomos, comoun grupo Øter poliglicólico. Otros
30 compuestos de amonio cuaternario polimerizables adecuados incluyen heterociclos de
nitrógeno cuaternizados sustituidos con vinilo como las sales de metilvinil piridinio, los Østeres de vinilo de Æcidosamino carboxIlicos cuaternizados y las sales de estiriltrialquilamonio. Otros compuestos de amonio cuaternario polimerizables ütiles en
la presente invención incluyen cloruro y metosulfato de acril- y metacril-
35 oxietiltrimetilamonio, cloruro de bencildimetilamoniometil-metacrilato, metosulfato de
dietilmetilamoniometil-acrilato y -metacrilato, cloruro de N-

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trimetilamoniopropilmetacrilamida, cloruro de N-trimetilarnonio-2,2-dimetilpropil- 1 metacrilato y sus rnezclas.

En al menos una realización, el polimero del recubrimiento de liberaciÆncontrolada es un
5 polimero acrIlico compuesto de uno o mÆs copolirnerosde metacrilato de amonio. Los
copoilmeros de metacrilato de amonio (por ejemplo, EUDRAGITfi RS y RL) se
describen en el National Formulary (NF) XVII como copolImeros totalmente
polimerizados de Østeres de Æcidoacrilico y metacrIlico con un bajo contenido de grupos amonio cuaternario. Para obtener un perfil de disoluciOn deseado para un principio
10 terapØuticamente activo dado, como bromhidrato de bupropion, puede ser ütil en algunas
realizaciones incorporar dos o mÆscopoilmeros de metacrilato de amonio con
propiedades fisicas diferentes. Pot ejemplo, Se sabe que cambiando la relaciOn molar
entre los grupos de amonio cuaternario y los Osteres (met)acrflicos neutros, se pueden modificar las propiedades de permeabilidad del recubrimiento de liberación controlada
15 resultante.

En otras realizaciones de la presente invencióu, el recubrimiento de polimero acrIlico
incluye ademªs un polimero cuya permeabilidad es dependiente del pH, como los
polImeros aniónicos sintetizados a partir del Æcido metacrulicoy el ester metilico del
20 Æcido metacrilico(por ejemplo, EUDRAGITfi L y EUDRAGITfi S). EUDRAGITfi L
es insoluble en Æcidosy agua pura, pero se torna cada vez rnÆspermeable por encima de
pH 5,0. EUDRAGITfi S es similar, excepto porque se torna cada vez mÆs permeablepor encima de pH 7. Los recubrimientos de polimero acrIlico hidrófobos tambiØn pueden
incluir un polimero que tenga carÆctercatiónico a base de metacrilato de
 25 dimetilaminoetilo y Østeres del Æcido metacriliconeutros (como EUDRAGITfi E). Los
recubrimientos de polimero acrulico hidrOfobos de ciertas realizaciones pueden incluir
ademÆs uncopolimero neutro a base de poli(met)acrilatos, como EUDRAGITfi NE.

En otras realizaciones de la invenciOn, el polimero de liberación controlada es una
30 dispersion de poii(acrilato de etilo, metacrilato de metilo) 2:1 (por ejemplo,
KOLLICOATfi EMM 30 D). En otras realizaciones, el polimero de liberaciOn
controlada puede ser un acetato polivinilico estabilizado con polivinilpirrolidona y lauril sulfato de sodio como KOLLICOATfi SR30D. El perfil de disolución se puede alterar cambiando las cantidades relativas de diferentes lacas de resina acrilica incluidas en el
35 recubrimiento. Asimismo, cambiando la relación molar entre el agente polimerizable que
mejora la permeabilidad (por ejemplo, los compuestos de amonio cuaternario) en ciertas

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realizaciones y los Østeres (met)acrflicos neutros, se pueden modificar las propiedades de permeabilidad (y por to tanto el perfil de disoluciOn) del recubrimiento resultante.

En at menos una realización el polimero de liberación controlada es etilcelulosa, que se
5 puede usar como un polimero seco (por ejemplo, ETHOCELfi) solubilizado en
disolvente orgÆnico antes deusar, o como una dispersion acuosa. Una dispersion acuosa comercialmente disponible de etilcelulosa es AQUACOATfi. El AQUACOATfi se
puede preparar disolviendo la etilcelulosa en un disolvente orgÆnicoinmiscible con agua
y luego etnulsionar el mismo en agua en presencia de un tensioactivo y un estabilizador.
10 DespuØs de la homogeneización para generar gotitas submicrOnicas, el disolvente
organico se evapora at vaclo para formar un pseudolÆtex. Elplastificante no se incorpora
en el pseudolÆtex durantela fase de fabricación. Por to tanto, antes de usar el mismo
como un recubrimiento, el AQUACOATfi se mezcla bien con un plastificante adecuado

40 antes de usar. Otra dispersion acuosa de etilcelulosa es SURELEASEfi. Este producto
15 se puede preparar incorporando un plastificante en la dispersion durante el proceso de
fabricaciOn. Se prepara una masa fundida caliente de un polimero, un plastificante (por
ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, Æcidooleico) como una
mezcla homogØnea, que luego se diluye con una solución alcalina para obtener una
dispersion acuosa que se.puede aplicar directamente sobre los sustratos.
20

Otros ejemplos de poilmeros que se pueden usar en el recubrimiento de liberaciOn
controlada incluyen ftalato acetato de celulosa, trimaleato acetato de celulosa, ftalato de hidroxipropilmetilcelulosa, ftalato acetato de polivinilo, ftalato de alcohol polivinilico,
laca; hidrogeles y materiales que forman geles, como polImeros carboxivinflicos, alginato
de sodio, carmelosa de sodio, carmelosa de calcio, carboximetil almidOn sódico, alcohol polivinilico, hidroxietilcelulosa, metilcelulosa, etilcelulosa, gelatina, almidón y polImeros reticulados a base de celulosa en los que el grado de reticulación es bajo para facilitar la adsorción de agua y la expansion de la matriz del polimero, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, almidOn reticulado, celulosa
30 microcristalina, quitina, pullulan, colÆgeno,caseIna, agar, goma arÆbiga,
carboximetilcelulosa sódica, (polImeros hidrófilos hinchables)
poli(hidroxialquilmetacrilato) (peso molecular de aproximadamente 5 k a
aproximadamente 5.000 k), polivinilpirrolidona (peso molecular de aproximadamente 10
k a aproximadamente 360 k), hidrogeles aniónicos y catiOnicos, zeIna, poliamidas,
35 alcohol polivinilico con bajo contenido de acetato residual, una mezcla hinchable de agar
y carboximetilcelulosa, copolImeros de anhIdrido maleico y estireno, etileno, propileno o isobutileno, pectina (peso molecular de aproximadamente 30 k a aproximadamente 300
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k), polisacÆridoscomo agar, acacia, karaya, tragacanto, alginas y guar, poliacrilainidas,
ó xidos de polietileno POLYOXfi (peso molecular de aproximadamente 100 k a
aproximadamente 5.000 k), polImeros de acrilato AQUAKEEPfi, diØsteres de poliglucano, alcohol polivinilico y poli N-vinil-2-pirrolidona reticulados, polimeros hidrOfilos como los polisacÆridos, metilcelulosa, carboximetilcelulosade sodio o de
calcio, hidroxipropilmetilcelulosa, hidroxipropilcelulosa, hidroxietilcelulosa,
nitrocelulosa, carboximetilcelulosa, Øteres de celulosa, metiletilcelulosa, etilhidroxietilcelulosa, acetato de celulosa, butirato de celulosa, propionato de celulosa, gelatina, almidOn, maltodextrina, puilulan, polivinilpirrolidona, alcohol polivinIlico,
10 acetato de polivinilo, Østeres de Æcidos grasosde glicerol, poliacrilamida, Æcido
poliacrilico, gomas naturales, lecitinas, pectina, alginatos, alginato de amonio, alginatos
de sodio, calcio y potasio, alginato de propilenglicol, agar y gomas corno arÆbiga,karaya,
de algarrobo, tragacanto, carrageninas, guar, xantano, escieroglucano y sus mezclas y combinaciones.
15
En al menos una realización, el recubrimiento de liberación controlada de las
micropartIculas comprende poilmeros que pueden facilitar la adhesion a la mucosa del
tubo digestivo. Ejemplos no limitantes de polirneros que se pueden usar para la adhesion
a la mucosa incluyen carboximetilcelulosa, ªcido poliacrifico, CARBOPOLTM,
20 POLYCARBOPHILTM, gelatina y otros polIrneros naturales o sintØticos.

En al menos una realización las microparticulas se recubren con un recubrimiento de
liberaciOn controlada compuesto de: al menos un polimero formador de pelicula que es
insoluble en los liquidos del tubo digestivo, presente en una cantidad entre
1025 aproximadamente 50% y aproximadamente 90%, incluidos todos los valores y rangos
intermedios, (por ejemplo, entre aproximadamente 50% y aproximadamente 80%) en
peso de la materia seca de la composición del recubrimiento de liberaciOn controlada y
que incluya al menos un derivado de celulosa no hidrosoluble, (por ejemplo, etilcelulosa, acetato de celulosa o sus rnezclas); al menos un polImero que contiene nitrógeno,
30 presente en una cantidad entre aproximadamente 2% y aproximadamente 25%, incluidos
todos los valores y rangos intermedios (por ejemplo, entre aproximadamente 5% y aproximadamente 15%) en peso de la materia seca de la composición del recubrimiento
de liberaciOn controlada y que incluya al menos una poliacrilamida, poli-N-vinilamida, poli-N-vinil-lactama, polivinilpirrolidina o sus rnezclas; opcionalmente un plastificante
35 presente en una cantidad entre aproximadamente 2% y aproximadamente 20%, incluidos
todos los valores y rangos intermedios (por ejemplo, entre aproximadamente 4% y aproximadamente 15%) en peso de la materia seca de la composición del recubrimiento

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de liberación controlada y que incluya al menos uno de los compuestos siguientes:
Østeres, ftalatos, citratos y sebacatos de glicerol, Østeres de alcohol cetilico, aceite de
ricino, cutina o sus xnezclas; al menos un agente de superficie y/o un lubricante, presentes
en una cantidad entre aproximadamente 2% y aproximadamente 20%, incluidos todos los
5 valores y rangos intermedios, (por ejemplo, entre aproximadamente 4% y
aproximadamente 15%) en peso de la materia seca de la composición del recubrimiento
de liberación controlada y que se eligen entre los tensioactivos aniónicos como las sales
de Æcidos grasos de metales alcalinosy alcalinotØrreos, (por ejemplo, ÆcidoesteÆrico, Æcidooleico y sus mezclas), y/o entre los tensioactivos no iónicos como los Østeres
10 polioxietilenados de sorbitÆn, derivados polioxietilenados de aceite de ricino, y/o entre
los lubricantes como los estearatos (por ejemplo, estearatos de calcio, magnesio,
aluminio, cinc y sus mezclas), estearilfumaratos (pot ejemplo, estearilfumarato de sodio, behenato de glicerilo y sus mezclas); y mezelas de Østos;
donde las micropartIculas recubiertas se diseflan para set capaces de permanecer en el
15 intestino delgado durante un perlodo de al menos 5 horas aproximadamente; en ciertas
realizaciones a! menos 7 horas aproximadamente; y en ciertas realizaciones durante un perfodo entre aproximadamente 8 horas y aproximadamente 24 horas; de modo de
permitir la absorción del bromhidrato de bupropion durante al menos parte de su tiempo
en el intestino delgado.
20

En un ejemplo profØtico de esta realización de la invención, las xnicropartIculas se
recubren en un revestidor de lecho fluidizado con la solución de recubrimiento siguiente:
Eticelulosa aproximadamente 44,7 g
PVP aproximadamente 4,8 g
Aceite de ricino aproximadamente 4,8 g
Estearato de maguesioaproximadamente 6,1 g
Acetona aproximadamente 479 g
Isopranol aproximadamente 53 g

30 En otras realizaciones de la presente invenciOn, la liberaciOn del bromhidrato de
bupropion desde una formulación de liberación controlada puede estar influida ademªs,
es decir, ajustada a una velocidad deseada, por la adición de uno o mÆs formadoresde
poros al recubrimiento de liberaciOn controlada, donde los formadores de poros pueden
ser inorgÆnicosu orgÆnicosy pueden incluir materiales que Se pueden disolver, extract o
35 lixiviar del recubrimiento de liberación controlada en el ambiente de uso. DespuØs de la
exposición a lIquidos en el ainbiente de uso, los formadores de poros se disuelven, por ejemplo, y se forman canales y poros que se Henan con el lIquido ambiental. Por

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ejemplo, los formadores de poros pueden incluir uno o rnÆspolimeros hidrófilos solubles
en agua para modificar las caracterIsticas de liberación de la formulación. Los ejemplos
no limitantes de polimeros hidrófilos adecuados incluyen hidroxipropilmetilcelulosa,
Øteres de celulosa y derivados proteicos de estos polimeros, Øteres de celulosa, (por
5 ejemplo, hidroxialquilcelulosas y carboxialquilcelulosas) y sus mezclas. Ademªs, se
pueden usar polimeros solubles en agua sintØticos, como polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de polietileno, polidextrosa soluble en agua, sacÆridosy polisacÆridos, como pullulan,dextrano, sacarosa, glucosa, fructosa, manitol, lactosa, manosa, galactosa, sorbitol y sus rnezclas. En al menos una realización, el o los
10 polimeros hidrófilos comprenden hidroxipropilmetilcelulosa. Otros ejemplos de
formadores de poros incluyen sales de metales alcalinos como earbonato de litio, cloruro
de sodio, bromuro de sodio, cloruro de potasio, sulfato de potasio, fosfato de potasio,
acetato de sodio, citrato de sodio y sus rnezclas. Los sólidos formadores de poros
tarnbiØn pueden ser polimeros que son solubles en el arnbiente de uso, como los
15 CARBOWAXfi, CARBOPOLfi y similares. Los formadores de poros abarcan dioles,
polioles, aleoholes polihidricos, polialquilenglicoles, poliglicoles, poli(a-w)alquilendioles
y sus mezclas. Otros formadores de poros que pueden ser ütiles en las formulaciones de
la presente invenciOn incluyen almidón, alrnidón modificado y derivados del almidón,
gomas, incluidas, pero no exciusivamente, goma xantano, ªcido alginico, otros alginatos,
20 bentonita, veegurn (silicato de aluminio y magnesio), agar, goma guar, goma de
algarrobo, gorna arabiga, quince psyllium, semilla de lino, goma de quimbombo, arabinogalactano, pectina, goma tragacanto, escieroglucano, dextrano, amilosa,
amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de intercambio iónico,
. como polimetacrilato de potasio, carragenina, carragenina kappa, carragenina lambda,
25 goma karaya, goma biosintØtica, y sus mezelas. Otros formadores de poros incluyen
materiales ütiles para hacer lÆminasmicroporosas en los ambientes de uso, como policarbonatos compuestos de poliØsteres lineales del Æcidocarbónico en los que los
grupos carbonato reaparecen en la cadena polimØrica, materiales microporosos como
bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas, copoilmeros
30 modacrilicos microporosos, estireno-acrIlico microporoso y sus copoilmeros,
polisuifonas porosas, poli(vinilideno) halogenado, policloroØteres, poilmeros de acetal, poliØsteres preparados por esterificaciOn de un Æcido dicarboxIlicoo anhIdrido con un aiquilenpoliol, poli(sulfiwos de aiquileno), fenólicos, poliØsteres, polimeros porosos asimØtricos, polimeros olefinicos reticulados, homopolfmeros hidrOfilos microporosos,
35 copolimeros o interpolirneros con una menor densidad aparente y otros materiales
sirnilares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas),

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poli(benzimidazoles), colodión, proteinas regeneradas, poii(vinilpirrolidona) reticulada semisólida y sus mezcias.

En otras realizaciones se puede incluir un tensioactivo o una base efervescente en el
5 recubrimiento de iiberación controlada, ci cual puede reducir y en ciertas realizaciones
vencer los efectos de tension superficial. AdemÆs,ci recubrimiento de liberación
controlada de ciertas realizaciones puede incluir uno o mÆs osmoagentes (es decir,que pueden liberar osmóticamente ci principio activo desde ci dispositivo proporcionando un gradiente de presión osmótica contra los lIquidos externos), agentes de hinchamiento (es
10 decir, los cuales pueden incluir, pero no exciusivamente, compuestos hidrOfilos
farmacØuticamente aceptabies con diversas velocidades de hinchamiento en agua), u
otros agentes farmacØuticamente aceptables (es decir, provistos en una cantidad
suficiente para facilitar ci ingreso de liquido ambiental sin causar la alteración del recubrimiento impermeable). Los tensioactivos que se pueden usar en ci recubrimiento
15 de liberación controlada de ciertas realizaciones pueden ser aniónicos, catiOnicos, no
iOnicos o anfóteros. Los ejemplos no limitantes de dichos tensioactivos incluyen lauril sulfato de sodio, dodecil sulfato de sodio, Østeres de sorbitÆn,polisorbatos, piurónicos,
laurato de potasio y sus mezelas. Los ejemplos no limitantes de bases efervescentes que
se pueden usar en ci recubrimiento de liberación controlada de ciertas realizaciones
20 incluyen carbonato de glicina sódica, carbonato de sodio, carbonato de potasio,
bicarbonato de sodio, bicarbonato de potasio, bicarbonato de calcio y sus mezelas. Los ejemplos no limitantes de osmoagentes que se pueden usar en ci recubrimiento de
liberación controlada de ciertas realizaciones incluyen cioruro de sodio, cloruro de calcio,
lactato de calcio, sulfato de sodio, lactosa, glucosa, sacarosa, manitol, urea, otros
W5 compuestos orgÆnicose inorgÆnicosconocidos en ci drea y sus mezclas. El agente de
hinchamiento puede incluir, pero no exciusivamente, al menos un compuesto hidrófilo farmacØuticamente aceptable, con una tasa de hinchamiento o una cantidad de
hinchamiento en agua a. aproximadamente 25°C que es: mayor o igual que al menos aproximadamente 10% en peso (p/p), mayor o igual que al menos aproximadamente 15%
30 en peso (pip), o mayor o igual que al menos aproximadamente 20% en peso (p/p). Los
ejemplos no limitantes de agentes de hinchamiento que se pueden usar en ci
recubrimiento de liberación controlada de ciertas realizaciones de la presente invención incluyen polovinilpirrolidonas reticuiadas (por ejemplo, poliplasdona, crospovidona y sus mezcias), carboxiaiquiicelulosas reticuladas, carboximetilceiuiosa reticulada (por
35 ejemplo, crosearmelosa sódica reticulada), poilmeros hidrófilos de masa molar elevada
(es decir, que pueden ser, pero no exciusivamente, mayores o iguales que 100.000
Daltons) los que pueden incluir, pero no exciusivamente: polivinilpirrolidona(s) Oxidos

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de polialquileno (por ejemplo, óxido de polietileno, óxido de polipropileno y sus
mezelas), hidroxialquilceiulosas (por ejemplo, hidroxipropilcelulosa, hidroxipropilmetilcelulosa y sus mezclas), carboxialquilcelulosa (por ejemplo, carboximetilcelulosa), almidOn modificado (por ejemplo, glicolato de sodio), alinidón o
5 almidón natural (por ejemplo, de maIz, de trigo, de arroz, de papa y sus mezclas),
celulosa (es decir que puede estar, pero no exciusivamente, en forma de polvo o en forma microcristalina), alginato de sodio, polacrilina potÆsicay sus correspondientes combinaciones o rnezclas. En otras realizaciones, los ejemplos no limitantes de agentes
de hinchamiento inciuyen los subconjuntos de compuestos siguientes:
10 polovinilpirrolidona reticulada (por ejemplo, poliplasdona, crospovidona o sus niezclas),
earboxialquilcelulosas reticuladas (por ejemplo, carboxirnetilcelulosas reticuladas corno croscarmelosa sódica reticulada) y sus mezelas. En otras realizaciones, el agente de hinchamiento puede ser un poilmero que contiene nitrógeno, cuyos ejemplos no
limitantes pueden incluir polivinilpirrolidona, polivinilpirrolidona reticulada y sus
15 mezelas. La concentración de agente de hinchamiento en el recubrimiento de liberación
controlada de ciertas realizaciones de la presente inveneión puede estar entre aproximadamente 3% y aproximadamente 40% en peso de la microparticula, incluidos
todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones la concentración del agente de hinchamiento en el recubrimiento de liberación controlada es
20 de aproximadamente 4% a aproximadamente 30%, y en otras realizaciones de
aproximadamente 5% a aproximadamente 25% en peso de la microparticula.

En ciertas realizaciones se pueden usar, uno o mÆsexcipientes farmacØuticarnente
aceptables compatibles con los objetivos de la presente invenciOn en el recubrimiento de
25 liberación controlada, como un lubricante, un emulsionante, un antiespumante y/o un
plastificante.

Se pueden incluir lubricantes en cl recubrimiento de liberación controlada para ayudar a reducir la fricción de las micropartleulas recubiertas durante la fabricación. Los
30 lubricantes que Se pueden usar en el recubrimiento de liberación controlada de ciertas
realizaciones de la presente invención incluyen, pero no exelusivamente, Æcido adipico, estearato de magnesio, estearato de caicio, estearato de cinc, silicato de calcio, silicato de magnesio, aceites vegetales hidrogenados, cloruro de sodio, esterotex, polioxietileno, monoestearato de glicerilo, talco, polietilenglicol, benzoato de sodio, lauril sulfato de
35 sodio, lauril sulfato de magnesio, estearil fumarato de sodio, aceite mineral ligero, Østeres
de Æcidos grasoscomo behenato de glicerilo, (por ejemplo COMPRITOLTM), STEAR-O-WETTM y MYVATEXTM TL. En al menos una realización, ci lubricante se selecciona

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entre estearato de magnesio, talco y sus mezclas. Las combinaciones de estos lubricantes son factibles. Cada lubricante puede estar presente en una cantidad entre
aproximadamente 1% y aproximadamente 100% en peso del peso seco del recubrimiento
de liberación controlada, incluidos todos los valores y rangos intermedios. Por ejemplo,
5 en ciertas realizaciones en las que el poilmero de liberaciOn controlada es EUDRAGITfi
NE3OD o EUDRAGITfi NE40D junto con un formador de poros hidrófilo, el lubricante estÆpresente en una cantidad entre aproximadamente 1% y aproximadamente 30% en
peso del peso seco del recubrimiento de liberación controlada; en otras realizaciones
entre aproximadamente 2% y aproximadamente 20%; y aun en otras realizaciones en
10 aproximadamente 10% en peso del peso seco del recubrimiento de liberación controlada
de la micropartIcula. En otras realizaciones donde el polimero de liberación controlada
es etilcelulosa (ETHOCELTM polImero PR100, PR45, PR20, PR1O o PR7, o una mezela
de los mismos), el lubricante puede estar presente en una cantidad entre
aproximadamente 10% y aproximadamente 100% en peso del peso seco del
15 recubrimiento de liberación controlada de la micropartleula; en otra realización entre
aproximadamente 20% y aproximadarnente 80%; y aun en otras realizaciones en aproximadamente 50% en peso del peso seco del recubrimiento de liberación controlada
de la micropartIcula.

20 Se pueden incluir uno o mªs emulsionantes (tambiØn denominados emulsionantes o
emulgentes) en el recubrimiento de liberación controlada de la micropartIcula para
facilitar la emulsificación real durante la fabricación del recubrimiento y tambiØn para
asegurar la estabilidad de la emulsion durante la vida ütil en depósito del produeto. Los emulsionantes ütiles para la composición del recubrimiento de liberaciOn controlada de la
025 micropartIcula incluyen, pero no exciusivamente, materiales de origen natural y sus
derivados semisintØticos, como los polisacaridos, asi como Østeres de glicerol, Øteres de
celulosa, Østeres de sorbitÆn (por ejemplo, monooleatode sorbitÆn oSPANTM 80) y
polisorbatos (jior ejemplo, TWEENTM 80). Las combinaciones de emulsionantes son
factibles. En al menos una realizaciOn, el emulsionante es TWEENTM 80. El o los
30 emulsionante(s) pueden estar presentes en una cantidad entre aproximadamente 0,01% y
aproximadamente 5% en peso del peso seco del recubrimiento de liberación controlada
de la micropartIcula, incluidos todos los valores y rarigos intermedios. Por ejemplo, en ciertas realizaciones el emulsionante estÆ presente en unacantidad entre
aproximadamente 0,05% y aproximadamente 3%; en otras realizaciones entre
35 aproximadamente 0,08% y aproximadamente 1,5%, y aun en otras realizaciones en
aproximadamente 0,1% en peso del peso seco del recubrimiento de liberación controlada
de la micropartIcula.

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Se pueden incluir uno o mÆsantiespuinantes en el recubrimiento de liberación controlada
de la microparticula para reducir la producciOn de burbujas o de espuma durante la fabricaciOn del recubrimiento. Los antiespuinantes ütiles para la cornposiciOn del
5 recubrimiento incluyen, pero no exciusivamente, simeticona, poliglicol y aceite de silicio.
En al menos una realización, el antiespumante es simeticona C. El antiespurnante puede
estar presente en una cantidad entre aproximadamente 0,1% y aproximadamente 10% del peso del recubrimiento de liberaeión controlada de la microparticula, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el antiespumante estÆ
10 presente en una cantidad entre aproximadamente 0,2% y aproximadamente 5%; en otras
realizaciones entre aproximadamente 0,3% y aproximadamente i% y aun en otras realizaciones en aproximadamente 0,6% en peso del peso seco del recubrimiento de liberación controlada de la microparticula.

15 Se pueden incluir uno o rnÆsplastificantes en el recubrimiento de liberación controlada
de la microparticula para modificar las propiedades y caracteristicas de los polimeros
usados en el recubrimiento para un procesamiento conveniente durante la fabricación
(por ejemplo para proporcionar mayor flexibilidad y durabilidad durante la fabricación).
El tØrmino "plastificante" como se usa aqul incluye todos los compuestos capaces de
20 plastificar o ablandar un polimero 0 Ufl aglutinante usados en la presente invención. Una
vez que se preparO el recubrimiento, ciertos plastificantes pueden actuar para aumentar la hidrofihicidad del recubrimiento en el ambiente de uso. Durante la fabricaciOn del recubrimiento, el plastificante puede disminuir la temperatura de fusion o la temperatura
de transición vitrea (temperatura del punto de ablandarniento) del pollinero o aglutinante.
25 La adición de un plastificante, como los PEG de bajo peso molecular, generalmente
amplIa ci peso molecular promedio de un poilmero en el cual estÆ incluido disminuyendo
de ese modo su temperatura de transición vitrea o punto de ablandamiento. Los
plastificantes tambiØn pueden generalmente reducir la viscosidad de un poilmero. Los ejemplos no lirnitantes de plastificantes que se pueden usar en el recubrimiento de
30 liberación controlada de la microparticula inciuyen monoglicØridos acetilados; acetil
tributil citrato, butil flalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dirnetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina;
diacetina; ftalato de dibutilo; monoglicØrido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de coiza, aceite de oliva, aceite de sØsarno,
35 citrato de trietilo; alcoholes polihidricos, glicerol, glicerina, sorbitol, Østeres de acetato,
triacetato de glicerol, acetil trietil citrato, ftalato de dibencilo, ftalato de dihexilo, octil ftalato de butilo, ftalato de di isononilo, octil ftalato de butilo, azelato de dioctilo, taiato

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epoxidado, trimelitato de triisoctilo; ftalato, de dietilhexilo, ftalato de di-n-octilo, ftalato
de di-i-oetilo, ftalato de di-i-decilo, ftalato de di-n-undecilo, ftalato de di-n-tridecilo, trimelitato de tri-2-etilhexilo, adipato de di-2-etilhexilo, sebacato de di-2-etilhexilo,
azelato de di-2-etilhexilo, sebacato de dibutilo, oxalato de dietilo, malato de dietilo,
5 fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo,
sebacato de dibutilo, tributirato de glicerol y sus mezelas. El plastificante puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 80% del peso seco del recubrimiento de liberación controlada, incluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones, el plastificante estÆ presenteen una
10 cantidad entre aproximadamente 5% y aproximadamente 50%, en otras realizaciones
entre aproximadamente 10% y aproximadamente 40% y aun en otras realizaciones en aproximadamente 20% del peso seco del recubrimiento de liberación controlada.

El recubrimiento de liberación controlada puede estar presente en una cantidad entre
15 aproximadamente 1% y aproximadamente 100% en peso de la mieropartIcula, incluidos
todos los valores y rangos intermedios, dependiendo de la elecciOn del polImero, la
relación polImero:formador de poros y el area superficial total de la formulación de la micropartIcula. Puesto que tiene que lograrse un cierto espesor del recubrimiento de liberación controlada para lograr el perfil de disolución deseado, la cantidad de
20 recubrimiento de pol{mero requerida durante la fabricación estÆ relacionada con el area
superficial total del lote de microparticulas sin recubrir que requiere un recubrimiento.
La cobertura de area superficial del polImero de liberación controlada puede variar de aproximadamente 0,5 mg/cm2 a aproximadamente 30 mg/cm2, incluidos todos los valores
y rangos intermedios. Por ejemplo, en ciertas realizaciones la cobertura de area
 5 superficial del polImero de liberación controlada es de aproximadamente 0,6 mg/cm2 a
aproximadamente 20 mg/cm2, y en otras realizaciones es de aproximadamente 1 mg/cm2
a aproximadamente 5 mg/cm2. En al menos una realización de la invención, se emplea EUDRAGITfi NE30D como el polImero de liberación controlada a una cobertura de area superficial de 10 mg/cm2. Un enfoque para estimar el area superficial total de un lote
30 multiparticulado es el mØtodo de permeabilidad segün Blame (ASTM Des. C 205-55),
que se basa en el modelo matemÆticode flujo laminar a travØs de capilares dispuestos en paralelo. A falta de una determinaeión exacta del area superficial total de una
micropartIcula, la cantidad de polImero de liberación controlada que se debe aplicar se
puede expresar como un porcentaje de la micropartIcula sin recubrir.
35

El polImero de liberación controlada puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 99% en peso de la micropartIcula recubierta,

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incluidos todos los valores y rangos intermedios, dependiendo del perfil de liberación controlada deseado. Por ejemplo, en ciertas realizaciones ci poilmero estÆpresente en
una cantidad entre aproximadamente 5% y aproximadamente 80%, y en otras
realizaciones entre aproximadamente 10% y aproximadamente 50% en peso de la
5 microparticula recubierta. En al menos una realización en la que el polimero de
iiberación controlada es EUDRAGITfi NE30D, EUDRAGITfi NE40D, KOLLICOATfi
SR 30D, o una mezela de 6stos, el polimero estÆ presente en unacantidad entre aproximadamente 1% y aproximadamente 50%; en otras realizaciones entre aproximadamente 5% y aproximadamente, 30%; y aun en otras realizaciones en
10 aproximadamente 15% en peso de la microparticula recubierta. En al menos una
realización en donde ci polimero de liberación controlada es etilcelulosa, ci polimero estÆ presente en una cantidad entre aproximadamente 1% y aproximadamente 99% en peso de
la microparticula recubierta; en otras realizaciones entre aproximadamente 5%y aproximadamente 50%; y aun en otras realizaciones en aproximadamente 20% en peso de
15 la microparticula recubierta. En al menos una realización en donde ci polimero de
liberación controlada es ETHOCELTM, una etilcelulosa polimero grado PR100, PR45,
PR20, PR1O, PR7 o una mezcla de Østos, ci polimero estÆpresente en una cantidad entre aproximadamente 5% y aproximadamente 30% en peso de la microparticula recubierta;
en otras realizaciones entre aproximadamente 10% y aproximadamente 25%; y aun en
20 otras realizaciones en aproximadamente 20% en peso de la microparticula recubierta.

En ciertas realizaciones, ci diÆmetro delas micropartIcuias (con o sin recubrimiento de liberación controlada) puede variar de aproximadamente 50 p.m a aproximadamente 800 jim, ineluidos todos los valores y rangos intermedios. Por ejemplo, en ciertas
25 realizaciones el diÆrnetro de las micropartleulasvarla de aproximadamente 100 p.m a
aproximadamente 600 p.m y en otras realizaciones de aproximadamente 150 p.m a aproximadamente 450 p.m.

Se contempia que en realizaciones alternativas, se pueden usar otros excipientes
30 compatibles con los objetivos de la presente invenciOn en ci recubrimiento de liberaciOn
controlada, de la microparticula.

En al menos una reaiización, ci recubrimiento de liberación controlada de la
microparticula incluye aproximadamente 96% de EUDRAGITfi NE30D,
35 aproximadamente 1,9% de estearato de magnesio, aproximadamente 1,9% de taico,
aproximadamente 0,04% de TWEEN 800 y aproximadamente, 0,19% de Simeticona C, cuando se expresa como porcentaje en peso de la composición del recubrimiento de

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liberación controlada seco. En otra realización, ci recubrimiento de iiberaciOn controlada
de la micropartIcula inciuye aproximadamente 68% de etilcelulosa, aproximadamente
17% de monoestearato de glicerilo y aproximadamente 15% de acetil tributil citrato,
cuando se expresa como porcentaje en peso de la composición del recubrimiento de
5 liberación controlada seco.

En ciertas realizaciones, ci recubrimiento de iiberación controlada de la micropartIcula se puede realizar de acuerdo con cualquiera de los mØtodos descritos en ci presente.

10 El proceso de fabricación del recubrimiento de iiberación controlada de la microparticula
puede ser el siguiente. Se divide agua en dos porciones de aproximadamente 15%y aproximadamente 85%. DespuØs se agregan ci antiespumante y ci emulsionante a la
porción de 15% de agua y se mezclan a 300 rpm para formar la porción A. En al menos
una reaiización, el antiespumante es Simeticona C y el emulsionante es TWEEMTM 80.
15 DespuØs se agrega un primer lubricante ala porciOn de 85% de agua y se mezcla a 9.500
rpm para formar la porción B. En al menos una realización, el primer lubricante es talco. DespuØs la porción A se mezcla con la porción B, se agrega lentamente un segundo
lubricante y se mezcla a aproximadamente 700 rpm durante toda la noche. En al menos
una reaiización, ci segundo lubricante es estearato de magnesio. Finaimente, se agrega
20 una dispersion acuosa de un copoilmero de un ester neutro y se mezcia durante
aproximadamente 30 minutos a aproximadamente 500 rpm. En al menos una realización,
la dispersion acuosa de un copoilmero de un ester neutro es EUDRAGITfi NE30D. La
soiución de recubrimiento de iiberación controlada resultante se puede usar entonces para recubrir las micropartIculas hasta tin aumento de peso de aproximadamente 35% con los
025 parÆmetrossiguientes: Una temperatura de entrada entre aproximadamente 10°C y
aproximadamente 60°C, incluidos todos los valores y rangos intermedios, en ciertas realizaciones, entre aproximadamente 20°C y aproximadamente 40°C, y en al menos una reaiizaciOn, entre aproximadamente 25°C y aproximadamente 35°C; una temperatura de
salida entre aproximadamente 10°C y aproximadamente 60°C, incluidos todos los valores
30 y rangos intermedios, en ciertas realizaciones, entre aproximadamente 20°C y
aproximadamente 40°C, y en al menos una reaiización, entre aproximadamente 25°C y aproximadamente 35°C; una temperatura del producto entre aproximadamente 10°C y aproximadamente 60°C, incluidos todos los valores y rangos intermedios, en ciertas realizaciones, entre aproximadamente 15°C y aproximadamente 35T, y en al menos una
35 reaiización, entre aproximadamente 22°C y aproximadamente 27°C; tin flujo de aire entre
aproximadamente 10 cm!h y aproximadamente 180 cm/h, incluidos todos los valores y rangos intermedios, en ciertas realizaciones, entre aproximadamente 40 cm!h y
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aproximadamente 120 cm/h y en al menos una realizaciOn, entre aproximadamente 60
cm/h y aproximadamente 80 rn/h; y una presión de pulverización entre aproximadamente 0,5 bar y aproximadamente 4,5 bar, incluidos todos los valores y rangos intermedios, en ciertas realizaciones, entre aproximadamente II bar y aproximadamente 3 bar y en al
5 menos una realizaciOn, de aproximadamente 2 bar. Las microparticulas resultantes
recubiertas con el recubrimiento de liberación controlada Se pueden descargar despuØs
desde la cÆmarade recubrimiento y curar en estufa con los parÆmetrossiguientes: Una temperatura de curado entre aproximadamente 20°C y aproximadamente 65°C, incluidos
todos los valores y rangos intermedios, en ciertas realizaciones, entre aproximadamente
10 30°C y aproximadamente 55°C, y en al menos una realizaciOn, de aproximadamente
40°C; y un tiempo de curado entre aproximadamente 2 horas y aproximadamente 120
horas, incluidos todos los valores y rangos intermedios, en ciertas realizaciones, entre .aproximadamente 10 horas y aproximadamente 40 horas, y en al menos una realización, de aproximadamente 24 horas. TarnbiØn se puede usar cualquier otra tecnologfa que de’
15 como resultado la formulaeión del recubrimiento de liberación controlada de la
micropartIcula compatible con los objetivos de la invención.

Formas farrnacØuticas de micropartIcula
Resultan formas farrnacØuticas muy ittiles cuando las micropartleulas hechas de las
20 composiciones que contienen una sal bromhidrato de bupropion, auxiliares de
esferonización y otros excipientes se recubren con uno o mÆs poilmeros de liberación controlada. Las inicroparticulas con el recubrimiento de liberación controlada se pueden dntonces combinar con una masa de excipientes y/o otros excipientes farmacØuticos y
. comprimir en forma de comprimidos. Los comprimidos convencionales se pueden
25 fabricar comprimiendo las microparticulas recubiertas con excipientes adecuados usando
tØcnicas de compresión conocidas. El perfil de disolución de las microparticulas con recubrimiento de liberación controlada no es afectado de manera importante por la
cornpresión de las microparticulas en forma de comprimidos. Las formas farmacØuticas resultantes se benefician de la facilidad de procesarniento asociada con el uso de masas
30 de excipientes y de las propiedades de liberación asociadas con microparticulas con un
recubrimiento de liberaciOn controlada. Alternativamente, con las microparticulas recubiertas Se pueden llenar cÆpsulas.

Las formas de administración de acuerdo con la invenciOn son adecuadas para la
35 administración oral. En ciertas realizaciones las formas de administración son
comprimidos y cÆpsulas. No obstante,la composición de la invención tambiØn puede tornar la forma de pelets, perlas o microcomprimidos, que despuØs se pueden colocar en

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cÆpsulaso comprimir en una forma farmacØutica sólida unitaria. Los tØdnicos con experiencia pueden preparar otras formas farmacØuticas sólidas orales como las
divulgadas aqul, a pesar del hecho de que dichas formas farmacØuticas sólidas orales
pueden ser mÆsdificiles de fabricar con fines comerciales.
5

La presente invención tambiØn contempla combinaciones de microparticulas recubiertas
de manera diferente para dat una forma farmacØutica a fin de ofrecer una diversidad de perfiles de liberación distintos. Por ejemplo, en ciertas realizaciones, se pueden combinar microparticulas con un perfil de liberación retardada con otras microparticulas que tienen
10 un perfil de liberación sostenida para proporcionar una formulación de bupropion de
liberación controlada de multiples componentes. AdemÆs, otrasrealizaciones pueden
incluir uno o xnÆs componentes adicionales de liberación inmediata de bupropion. El componente de liberación inmediata de bupropion puede tomar la forma de
microparticulas de bupropion sin recubrir o polvos; tambiØn son conocidas por los
15 tØcnicos las microparticulas de bupropion recubiertas con un recubrimiento de liheraciOn
inmediata muy soluble, como un recubrimiento tipo OPADRYfi, o una combinación de cualquiera de los anteriores. DespuØs los multiples componentes se pueden mezclar
juntos en la relación deseada y colocar en una cÆpsula opreparar como comprimidos.
Los ejemplos de formulaciones de bupropion de liberación controlada de multiples
20 componentes se describen en US 6,905,708.

TecnologIa de sorbición de la dosis
La presente invención tambiØn contempla un sistema de administración oral para liberar microparticulas que contienen bromhidrato de bupropion mezeladas con un liquido. Por
1025 ejemplo, se proporciona un sistema de administración oral que comprende una cÆmarade
la formulación del fÆrmaco hueca. Enal menos una realización, la cÆmara tieneun
primer y un segundo extremos y contiene una formulación en forma de microparticulas.
La formulación de fÆrmaco comprende bromhidrato de bupropion. El sistema comprende ademÆs un liquido quepasa por el retenedor de la formulaciOn del fÆrmaco en el primer
30 extremo de la cÆmara. Elretenedor evita la liberación de las microparticulas desde ci
primer extremo pennitiendo la entrada de liquido a la cÆmara. Enotras realizaciones, las microparticulas contenidas dentro de Ia cÆmara comprendenbromhidrato de bupropion y
al menos otro fÆrmaco.

35 Ciertas realizaciones de la presente invención proporcionan ademÆs un mØtodo para la
administraciOn por via oral de las microparticulas que contienen la formulación de bromhidrato de bupropion mezelada con un liquido. El mØtodo implica la introducciOn de

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microparticulas de la formulación de bromhidrato de bupropion en una cÆmara de administración del fÆrmaeohueca de un dispositivo de administración de fÆrmacos. La cÆmaratiene un primer extremo y un segundo extremo. El primer extremo de la cÆmara tiene un liquido que pasa por el retenedor de la formulaciOn del fÆrmaco. El dispositivo
5 de adrninistración del fÆrmaco tiene un primer y un segundo extremo. El primer extremo
del dispositivo de administración del fÆrmacose introduce en un liquido y el segundo extremo se introduce en la boca de un paciente. DespuØs el paciente aplica succiOn al
segundo extremo del dispositivo para provocar la administración del liquido y las microparticulas de la formulación de bromhidrato de bupropion en la boca del paciente.

10

El tØrmino "retenedor de la formulación del fÆrmaco" como se usa aqul, se refiere a una vÆlvula, obturadoro restricción o sirnilares que evita el pasaj e de la formulación del
. fÆrmacodesde el dispositivo. Por "liquido que pasa por el retenedor de la forrnulación del
fÆnnaco"se concibe una vÆlvula,obturador o restricción o similar que permite el pasaj e
15 de lfquidos pºro no permite el pasaje de otros ingredientes corno la formulación del
fÆrrnacoque estÆcontenida en el dispositivo de adrninistración.

El dispositivo dispensador de esta realización de la invenciOn tiene uso cuando es
ineonveniente o inseguro usar formas farmacØuticas orales sOlidas corno cÆpsulaso
20 comprimidos. Los dispositivos pueden ser particulannente ütiles en las poblaciones de
pacientes geriÆtricaso pediÆtricas pero tambiØn puedenser ittiles para los que tienen dificultad para tragar cÆpsulaso comprimidos. Durante un programa terapØutico, se
puede administrar al paciente un Unico dispositivo de administración o varios

25

dispositivos.

En general el dispositivo estÆ en laforma preparada antes de la colocación en un liquido.
En al menos una realización el dispositivo dispensador comprende una cÆmarade formulaciOn del fÆrmacohueca con un primer extremo y un segundo extremo.
Contenidos dentro de la cÆmara se encuentranla formulaciOn del färmaco y el liquido que
30 pasa por el retenedor de la forrnulación del fÆnnaco. El liquidoque pasa por el retenedor
de la formulación del frmaco comprende una restricción y un obturador unidireccional.
El diÆmetrode la abertura es mÆs pequefloque el obturador. En al menos una
realización la restricción se hace plegando un extremo de la cÆmara. El segundoextremo
de la cÆmara tiene unretenedor de la formulación del fÆrmacopara evitar la liberaciOn
35 del obturador. En al menos una realizaciOn el retenedor se prepara plegando el extremo
de la cÆmara. DespuØslas microparticulas de brornhidrato de bupropion se colocan en la carnara. Se coloca una tapa sobre el segundo extremo de la eÆmaraantes de usar para

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evitar la liberación de la formulación del fÆrmaco. En laforma preparada, el obturador prÆcticamente sella elprimer extremo de la cÆmara, evitando de esemodo la pØrdida de la formulaeión del fÆrmaco por elprimer extremo.

5 El dispositivo se puede elaborar de cualquier material adecuado que sea fisica yb
qulmicamente compatible tanto con el fÆrmaco activocomo con el diluyente lIquido que
se va a mezclar aill. En ciertas realizaciones, los materiales representativos para elaborar dispositivos incluida la cÆmara dela formulación del fÆrmaco, el miembro tubular
alargado, las tapas y las lengUetas, incluyen, sin limitación, papel, plÆsticocomo
10 copolImeros de propileno/estireno, polipropileno, polietileno de alta densidad, polietileno
de baja densidad y similares. Los dispositivos pueden tener un diÆmetrointerno entre aproximadamente 3 mm y aproximadamente 8 mm, incluidos todos los valores y rangos intermedios, y un espesor de pared entre aproximadamente 0,1 mm y aproximadamente
0,4 mm, incluidos todos los valores y rangos intermedios. Los dispositivos pueden tener
15 entre aproximadamente 10 cm y aproximadamente 30 cm de longitud, incluidos todos los
valores y rangos intermedios.

El 11quido que pasa por el retenedor de la formulación del fÆrmaco permite el flujo libre
de medio lIquido pero prohIbe el pasaje de la formulaciOn del fÆrmaco desde el
20 dispositivo antes de la administración. Donde ci retenedor comprende un obturador
unidireccional o vÆlvula,el obturador o la vÆlvula sellarÆnla paja a la presión
atmosfØrica. Cuando se aplica succión, el lIquido se hace ilegar airededor del obturador y
dentro de la cÆmara dela formulación del fÆrmaco. AdemÆs, elobturador tiene una
densidad de menos de uno de modo que ascenderÆ a laparte superior a medida que la
 5 formulación del fÆrmaco se administraen la cavidad bucaL Cuando ya no Se aplique
succiOn, el obturador quedarÆ enla posiciOn mÆsalta que alcanzó durante la sorbición.
El obturador se puede preparar de espuma de polietileno de ceida cerrada como
ETHAFOAMfi. Otras formas de obturador unidireccional pueden ser un globo del
material elastomØrico, una valvula de bola mecÆnicaunidireccional y similares.
30

Los ejemplos de lIquido que se pueden usar para suspender la formulación del fªrmaco sorbiendo a travØs de la cÆmara deformulación del fÆrmaco incluye cualquier lIquido de sabor agradable como agua, jugo, leche, soda, cafØ, tØ, etc. Se debe tener cuidado de asegurar la compatibilidad del lIquido eon la formulación del fÆrmaco.

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En al menos una realización, un dispositivo de administración por sorbición de la dosis
de acuerdo con la presente invenciOn se puede preparar del modo siguiente. Se

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term.osellan pajas de tamafio Jumbo con un dirnetro interno de aproxirnadamente 0,21 pulgadas y una longitud de aproximadarnente 8 pulgadas a un extremo. El sello se corta parcialmente para que el obturador "unidireccional" no pueda escaparse. Se encierra el extremo parcialmente sellado en media cÆpsula degelatina dura. DespuØs se colocan las micropartIculas dentro del extremo, abierto de la paja. Se recorta un obturador "unidireccional" hecho de espuma de polietileno de celdas cerradas (por ej emplo, MICROFOAMfi) para que se ajuste convenienternente dentro de la paja. DespuØs el obturador se coloca dentro de la paja, ençirna de las microparticulas. Durante la
operación, el extremo del obturador de la paja se coloca en un vaso de agua y se retira la
10 cÆpsula de gelatina protectora dela parte superior de la paja. Al aplicar succion
lentamente a travØs del extremo parcialmente sellado de la paj a, las micropartIculas se succionan en la boca y se tragan fÆcilrnente.

Formas farmacØuticas osmóticas
15 Las formas farmacØuticas osrnóticas, los dispositivos de administración osmótica, las
formas farmaeØuticas osmóticas de liberaciOn modificada o los sistemas de liberaciOn

extendida controlada por osmosis son tØrminos usados aqul indistintamente y se definen para significar formas farrnacØuticas que dispensan forzadamente la sal bromhidrato de bupropion por la presión creada por osmosis o por Osmosis y difusiOn del lIquido en un
20 material que se expande y fuerza que la sal bromhidrato de bupropion se dispense desde
la forma farmacØutica osmótica. La osmosis se puede definir como el flujo de disolvente
de un compartimiento con una concentraciOn baja del soluto a un compartimiento con
una concentraciOn alta del soluto. Los dos compartirnientos estÆn separadospot una membrana, pared o recubrimiento, que permite el fiujo del disolvente (un lIquido, medio
25 acuoso, o lIquidos biológicos) pero no del soluto. Los ejeinpios no lirnitantes de dichas
membranas incluyen una membrana semipermeable, microporosa, membrana asimØtrica, donde la membrana asimØtrica puede ser permeable, semipermeable, perforada o no perforada. Dicha membrana puede administrar la sal bromhidrato de bupropion mediante bornbeo osmótico, difusiOn o los mecanismos combinados de difusión y boinbeo
30 osmOtico. Por lo tanto, en principio, la liberaciOn controlada por osmosis de la sal
bromhidrato de bupropion implica el transporte osmOtico de un medio acuoso al interior
de la forma farmacØutica osmOtica seguido de la disolución de la sal bromhidrato de bupropion y el transporte posterior de la solución saturada de la sal bromhidrato de bupropion mediante bombeo osmótico de la solución a travØs de al menos un pasadizo en
35 la membrana semipermeable o mediante una cornbinaciOn de Osmosis y difusiOn a travØs
de la membrana semipermeable.

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Es bien sabido por los tØcnicos con experiencia que la velocidad de liberación deseada in vitro y los parÆmetrosfarmacocinØticos in vivo pueden ser influidos por varios factores, como por ejemplo, la cantidad de sal bromhidrato de bupropion usada para formar el
nücleo, la cantidad de excipiente farmacØuticamente aceptable usado para formar el
5 nücleo, el tipo de excipiente farmacØuticamente aceptable usado para formar el nücleo, la
cantidad o el tipo de otros materiales usados para formar ci ni’ieleo como, por ejemplo, osmoagentes (las expresiones osmoagente, solutos osmOticamente eficaces, compuesto osmóticamente eficaz y agentes osmóticos se usan aqul indistintamente) osmopoilmeros
y cualquier combinación de Østos. El perfil de liberación tambiØn puede ser influido por
10 el material usado para formar la membrana semipermeable que cubre el nücleo o por el
material usado para formar cuaiquier recubrimiento, como un recubrirniento de liberación controlada. Con estos factores en mente, se puede diseæar por consiguiente un
dispositivo osmótico para que presente una velocidad de liberación in vitro tal que en
ciertas realizaciones, despuØs de aproximadamente 2 horas se libere de aproximadamente
15 0 a aproximadamente 20% en peso de la sal bromhidrato de bupropion, despuØs de
aproximadamente 4 horas se libere de aproximadamente 15% a aproximadamente 45%
en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se
libere de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato
de bupropion y despuØs de aproximadamente 16 horas, se libere mÆs de
20 aproximadamente 80% en peso de la sal bromhidrato de bupropion, cuando se mide por
ejemplo usando un aparatO tipo 1 de la USP (MØtodo de cesta rotatoria) en 900 ml de
agua, HC1 0,1 N, HC1 0,1 N + Cetrimida al 0,1%, solución amortiguadora USP de pH 1,5, soluciOn amortiguadora de acetato de pH 4,5, soiución amortiguadora de fosfato de pH
6,5 o solución amortiguadora de fosfato de pH 7,4 a 75 rpm a 37’C::L 0,5°C.
1025 Alternativamente, la disoiución se puede efectuar en los medios USP-3 como LOS de p1-I
1,2, solución amortiguadora de acetato de pH 4,5 o solución amortiguadora de fosfato de
p116,8.

TambiØn se pueden disefiar dispositivos osmóticos para lograr una iiberación in vitro de
30 no mÆs de aproximadamente 40% despuØs de aproximadamente2 horas, una liberación
de aproximadamente 40% a aproximadamente 75% despuØs de aproximadamente 4
horas, al menos una liberación de aproximadamente 75% despuØs de aproximadamente 8 horas y al menos una liberación de aproximadamente 85% despuØs de aproximadamente
16 horas cuando se analiza usando un medio de disolución como ci identificado antes o
35 conocido en el area.

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En ciertas realizaciones de la presente invención, se proporciona una forma farrnacØutica osmótica que tiene un nücleo que comprende la Sal bromhidrato de bupropion y uno o
rnÆs excipientes. En al menos unarealización la forma farmacØutica osmótica comprende
un osmoagente. El sistema de administración osmótica por ejemplo, puede estar en
5 forma de un comprimido o una cÆpsulaque contiene micropartIculas.

En ciertas realizaciones, el nücleo de la forma farmacØutica osmótica comprende un
poilmero hinchable en agua, cuyos ejemplos no limitantes incluyen hidroxipropilcelulosa, aiquilcelulosa, hidroxialquilcelulosa, óxido de polialquileno, óxido de polietileno y sus
10 mezclas. Se puede incluir un aglutinante en el nU.cleo de ciertas realizaciones de la forma
farmacØutica osmótica para aumentar la fuerza mecÆnica del nücleo. Los ejemplos no limitantes de aglutinantes incluyen polivinilpirrolidona, polImero carboxivinIlico, metilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, un polImero de Oxido de polietileno de bajo peso molecular, hidroxipropilmetilcelulosa,
15 dextrina, maltodextrina, gelatina, alcohol polivinilico, goma xantano, carbómeros,
carragenina, derivados del aimidón y sus mezclas. Se pueden incluir lubricantes en
ciertas reÆlizacionesde la forma farmacØutica osrnOtica para proporcionar una fricción reducida entre el sólido y la pared de la matriz durante la fabricación de comprimidos.
Los ejemplos no limitantes de lubricantes incluyen ÆcidoesteÆrico, estearato de
20 magnesio, behenato de glicerilo, talco, aceite mineral, estearil fumarato de sodio, aceite
vegetal hidrogenado, benzoato de sodio, estearato de calcio y sus mezclas. En otras realizaciones, se pueden incluir otros excipientes inertes compatibles con los objetivos de
la invenciOn en el nücleo de la forma farmacØutica osmótica para facilitar la preparación
y/o mejorar la aceptabilidad por el paciente de la forma farmacØutica osmótica final
25 segün se describe aqul. Los excipientes inertes adecuados son bien conocidos por los
tØcnicos con experiencia y se pueden encontrar en la bibliografia pertinente, por ejemplo
en el Handbook of Pharmaceutical Excipients (Rowe et al., 4’ Ed., Pharmaceutical Press, 2003).

30 En al menos una realización, la forma farmacØutica osmótica de liberación modificada
comprende brornhidrato de bupropion presente en una cantidad terapØuticamente eficaz la cual libera ci bromhidrato de bupropion dispensando forzadamente el bromhidrato de bupropion desde el nücleo a travØs de una membrana semipermeable mediante difusión
y/o a travØs de al menos un pasadizo en la membrana por bombeo osinótico (i) todo o en
35 pai-te mediante la presión creada en el nücleo por osmosis, es decir, presión hidrostÆtica
positiva de un lIquido, disolvente, liquido biolOgico o medios acuosos y/o todo o en parte
por expansion de un material hinchable que fuerza la dispensación del bromhidrato de

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bupropion desde el nücleo de la forma farmacØutiea, y (ii) se formula de tal manera que
la forma farmacØutiea presenta una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera
5 de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆs deaproximadamente 80% en peso de la sal bromhidrato de bupropion.
10

En al menos una realización, la forma farmacØutica de liberación modificada comprende
un dispositivo de administración osmótica, que comprende un nücleo sólido homogØneo
que contiene fundamentalmente la sal bromhidrato de bupropion en una cantidad terapØuticamente eficaz con al menos un excipiente farmacØuticamente aceptable, donde
15 dicho nücleo estÆ rodeado poruna membrana semipermeable que perrnite el ingreso de
un lIquido acuoso en el nücleo y la salida de la sal bromhidrato de bupropion desde ci
nücleo hacia el exterior de la forma farmacØutica a travØs de al menos un pasadizo o por combinación de osmosis y difusión de manera tal que la forma farmacØutica presenta una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de
20 aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se
025 libera mÆs deaproximadamente 80% en peso de la sal bromhidrato de bupropion. En al
menos una realización, la velocidad de liberación in vitro de la sal bromhidrato de
bupropion es tal que despuØs de aproximadamente 2 horas, se libera no mÆs de aproximadamente 40%, despuØs de aproximadamente 4 horas, se libera de
aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas,
30 se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 horas, se
libera al menos aproximadamente 85%.

En al menos una realización, la forma farmacØutica de liberación modificada comprende una forma famiacØutica multiparticulada, en la que cada microparticula comprende un
35 dispositivo de administración osmótica, donde cada micropartIcula comprende un nücleo
sólido homogØneo que contiene fundamentalmente la sal bromhidrato de bupropion con
al menos un excipiente farmacØuticamente aceptable, donde dicho nücleo de cada

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microparticula estÆ rodeadopor una membrana semipermeable que permite el ingreso de
un liquido acuoso en el nücleo y la salida de la sal bromhidrato de bupropion desde el
nüeleo hacia el exterior de la forma farmacØutica a travØs de numerosos poros formados
en la membrana semipermeable por inclusion de un formador de poros en la membrana o
5 por combinaciOn de Osmosis y difusiOn para permitir la comunicaciOn del nücleo con ci
exterior del dispositivo para la administración de la sal bromhidrato de bupropion y se formula de manera tal que la forma farmacØutica comprende una cantidad
terapØuticamente eficaz de la sal bromhidrato de bupropion y presenta una velocidad de liberaciOn in vitro tal que despuØs de aproximadamente 2 horas se libera de
10 aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, Se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuºs de aproximadamente 16 horas, se
15 libera rnÆsde aproximadamente 80% en peso de la sal bromhidrato de bupropion. En al
menos una realizaciOn, la velocidad de liberación in vitro de la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas, se libera no mÆs de aproximadamente 40%, despuØs de aproximadamente 4 horas, se libera de
aproximadamente 40% a aproximadamente 75%, despuºs de aproximadamente 8 horas,
20 se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 horas, se
libera al menos aproximadamente 85%.

En al menos una realización, la forma farmacØutica de liberaeión modificada comprende
. una forma farmacØutica multiparticulada, en la que cada microparticula comprende tin
25 dispositivo de adrninistraciOn osmOtica, donde cada microparticula comprende un nücleo
sOiido homogØneo que contiene fundamentalmente la sal bromhidrato de bupropion
mezclada con al menos un excipiente farmacØutieamente aceptable, un os.moagente yb
un osmopoilmero, donde dicho nüc!eo de cada microparticula estÆrodeado por una
membrana semipermeable que permite el ingreso de un lIquido acuoso en el nücleo y la
30 salida de la sal bromhidrato de bupropion desde ci nücleo hacia el exterior de la forma
farmaeºutica a travs de numerosos poros formados en la membrana semipermeable por inclusion de un formador de poros en la membrana o por combinaciOn de osmosis y
difusión para permitir la comunicación del nU.cleo con el exterior del dispositivo de administración de la sal bromhidrato de bupropion y se formula de manera tal que la
35 forma farmacØutica contenga una cantidad terapØuticamente eficaz de la sal bromhidrato
de bupropion y presente una velocidad de liberaciOn in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en

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peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mªs de aproximadamente 80% en peso de la Sal bromhidrato de bupropion. En al menos una realización, la velocidad de liberaeión in
vitro de la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas,
se libera no mªs de aproximadamente 40%, despuØs de aproximadamente 4 horas, se
libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente
10 8 horas, se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16
horas, se libera al menos aproximadamente 85%.

En al menos una realización, la forma farmacØutica de liberación modificada comprende
una forma farmacØutica multiparticulada, en la que cada micropartIcula comprende un
15 nócleo sólido homogØneo que contiene fundamentalmente la sal bromhidrato de
bupropion con al menos un excipiente farmacØuticamente aceptable mezclado con un osmoagente y/o un osmopolIrnero y/o un potenciador de la absorción, donde dichas microparticulas se comprimen en forma de un comprimido junto con al menos un
excipiente farmacØuticamente aceptable, donde dicho comprimido estÆ rodeado por una
20 membrana semipermeable que permite el ingreso de un liquido acuoso en el nücleo y la
salida de la sal bromhidrato de bupropion desde el interior del comprimido hacia ci
exterior de la forma farmacØutica a travØs de al menos un pasadizo en la membrana semipermeable y/o por difusión a travØs de la membrana semipermeable para permitir la comunicaciOn del interior del comprimido con el exterior del comprimido para la
05 administración de la sal bromhidrato de bupropion y se formula de manera tal que la
forma farmacØutica contenga una cantidad terapØuticamente eficaz de la sal bromhidrato
de bupropion y presente una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en
peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera
30 de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆsde aproximadamente 80% en peso de la sal bromhidrato de bupropion. En al menos una reaiizaciOn, ci perfil de iiberación in vitro de
35 la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas se libera
no mÆs de aproximadamente40%, despuØs de aproximadamente 4 horas se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas se
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libera al menos aproximadamente 75% y despuØs de aproximadamente 16 horas se libera
al menos aproximadamente, 85%.

En al menos una realizaciOn, la forma farrnacØutica de liberación modifleada comprende
5 una forma farmacØutica multiparticulada, en la que cada micropartIcula contiene una
esfera de azücar o una perla sin color recubierta eon al menos una capa que contiene fundamentalmente la sal brornhidrato de bupropion con al menos un excipiente farmacØuticarnente aceptable, donde dicha al menos una capa estÆ rodeadapor una membrana semipermeable que permite el ingreso de un lIquido acuoso en la capa y la
10 salida de la sal brornhidrato de bupropion desde la capa hacia el exterior de la forma
farmaeØutica a travØs de nurnerosos poros formados en la membrana semipermeable por inclusion de un formador de poros en la membrana y/o por difusión para permitir la comunicación del nücleo con el exterior del dispositivo para la administraciOn de la sal brornhidrato de bupropion y se formula de manera que la forma farmacØutica contenga
15 una cantidad terapØuticamente eficaz de la sal brornhidrato, de bupropion y presente una
velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal brornhidrato de bupropion, despuØs de
20 aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆs deaproximadamente 80% en peso de la sal brornhidrato, de bupropion. En al menos una realización, el perfil de liberaciOn in vitro de la sal brornhidrato de bupropion
es tal que despuØs de aproximadamente 2 horas, se libera no mÆs deaproximadamente
25 40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a
aproximadamente 75%, despuØs de aproximadamente 8 horas, se libera al menos aproximadamente 75%, y despues de aproximadamente 16 horas, se libera al menos aproximadamente 85%.

30 En al menos una realización, la forma farmacØutica de liberación modificada comprende
una forma farmacØutica multiparticulada, en la que cada rnicropartfcula contiene una
esfera de azücar o una perla sin color recubierta con al menos una capa que contiene fundamentalmente la sal brornhidrato de bupropion con al menos un excipiente fannacØuticamente aceptable, un osmoagente y/o un osmopolimero, donde dieha al
35 menos una capa estÆrodeada por una membrana semipermeable que permite el ingreso
de un liquido acuoso en la capa y la salida de la sal brornhidrato de bupropion desde la
capa hacia el exterior de la forma farmacØutica a travØs de numerosos poros formados en

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la membrana semipermeable por inclusion de un formador de poros en la membrana yb
por difusión para permitir la comunieaciOn del nücleo con el exterior del dispositivo para
la administraciOn de la sal bromhidrato de bupropion y se formula de manera que la
forma farmacØutica contenga una cantidad terapØuticamente eficaz de la sal bromhidrato
5 de bupropion y presente una velocidad de liberación in vitro tal que despuØs de
aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera
de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a
10 aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de
aproximadamente 16 horas, se libera mÆs deaproximadamente 80% en peso de la sal bromhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de
la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas se libera
no mÆs de aproximadamente40%, despuØs de aproximadamente 4 horas se libera de
15 aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas se
libera al menos aproximadamente 75% y despuØs de aproximadamente 16 horas se libera
al menos aproximadamente 85%.

En al menos una realizaciOn, la forma farmacØutica de liberaciOn modificada comprende
20 una forma farmacØutiea osmótica de liberaciOn modificada, que comprende un nücleo
homogeneo, que contiene una cantidad terapØuticamente eficaz de la sal bromhidrato de bupropion, mezelada con al menos un osmoagente y/o un osmopolImero, y/o un
potenciador de la absorción, donde dicho nücleo estª rodeado por una pared, membrana o recubrimiento atOxico, como por ejemplo, una membrana semipermeable que permite el
 25 ingreso de un lIquido acuoso en el nücleo y la salida de la sal bromhidrato de bupropion
desde el nücleo hacia el exterior de la forma farmacØutica a travØs de al menos un
pasadizo en la membrana semipermeable yio por difusiOn a travØs de la membrana para
permitir la comunicación del nücleo con el exterior de la forma farmacØutica para la administración de la sal bromhidrato de bupropion y se formula de manera que la forma
30 farmacØutica presente una velocidad de liberaciOn in vitro tal que despuØs de
aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera
de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a
35 aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de
aproximadamente 16 horas, se libera mÆs de aproximadamente80% en peso de la sal bromhidrato de bupropion. En al menos una realización, el perifi de liberación in vitro de

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la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas se libera
no mÆsde aproximadamente 40%, despuØs de aproximadamente 4 horas se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas se libera al menos aproximadamente 75% y despuØs de aproximadamente 16 horas se libera
5 al menos aproximadamente 85%.

En al menos una realización, la forma farmaeØutica de liberación modificada comprende
un dispositivo de administración osmótica, donde la sal bromhidrato de bupropion estÆ presente en una cantidad terapØuticamente eficaz distribuida en capas en contacto con una
10 composición de material hinchable para producir un nücleo sólido con dos o mÆs capas,
donde dicho nücleo estÆ rodeado por unapared, membrana o recubrimiento atóxico,
como por ejemplo, una membrana semipermeable que permite ci ingreso de un liquido acuoso en el nücleo y la salida de la sal bromhidrato de bupropion desde ci nücleo hacia
el exterior de la forma farmacØutica a travØs de al menos un pasadizo en la membrana
15 semipermeable o por osmosis y difusiOn a travØs de la membrana para permitir la
comunicación del nieleo con el exterior de la forma fannacØutica para la administración
de la sal bromhidrato de bupropion y se formula de manera que la forma farmacØutica presente una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas
Se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato
20 de bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a
aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuds de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆsde aproximadamente 80% en peso de la sal bromhidrato de bupropion. En al
25 menos una realización, el perfil de liberación in vitro de la sal bromhidrato de bupropion
es tal que despuds de aproximadamente 2 horas se libera no mÆs deaproximadamente
40%, despuØs de aproximadamente 4 horas se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas se libera al menos. aproximadamente 75% y despuØs de aproximadamente 16 horas Se libera al menos
30 aproximadamente 85%.

En al menos una realizaciOn, la forma farmacØutica de liberaciOn modificada comprende
un dispositivo de administraciOn osmótica, que incluye un nücleo y una membrana que lo rodea, donde dicho nücleo comprende una cantidad terapØuticamente eficaz de la sal
35 bromhidrato de bupropion y opcionalmente al menos un medio para dispensar
forzadamente la sal bromhidrato de bupropion desde el dispositivo, donde dicha
membrana comprende al menos un medio para la salida del sal bromhidrato de bupropion

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desde el dispositivo, estando dicho dispositivo formulado de forma tal que cuando el dispositivo estª en un medio acuoso, la sal bromhidrato de bupropion y opcionalmente el
al menos un medio para dispensar forzadamente la sal bromhidrato de bupropion desde el dispositivo y el al menos un medio para la salida de la sal bromhidrato de bupropion
5 desde el dispositivo actüan cooperativamente para presentar una velocidad de liberación
in vitro tal que despues de 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato
de bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a
10 aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de
aproximadamente 16 horas, se libera mÆsde aproximadamente 80% en peso de la sal bromhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de
la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas, se libera
no mÆs deaproximadamente 40%, despues de aproximadamente 4 horas, Se libera de
15 aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas,
se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 boras, se
libera al menos aproximadamente 85%.

En al menos una reaiizaciOn, la forma farrnacØutica de iiberación modificada comprende
20 un dispositivo de administración osmótica, que iucluye un nücleo y una membrana que lo
rodea, donde dicho nücleo comprende una cantidad terapØuticamente eficaz de la sal bromhidrato de bupropion, al menos un medio para aumentar la presión hidrostÆtica
dentro de la membrana y opcionalmente al menos un medio para dispensar forzadamente
la sal bromhidrato de bupropion desde ci dispositivo, donde dicha membrana comprende
025 al menos un medio para la salida del sal bromhidrato de bupropion desde el dispositivo,
estando dicho dispositivo formulado de forma tal que cuando el dispositivo estÆen un
medio acuoso, el al menos un medio para aumentar la presión hidrostÆticadentro de la membrana y opcionalmente ci al menos un medio para dispensar forzadamente la sal bromhidrato de bupropion desde ci dispositivo y el al menos un medio para la salida de la
30 sal bromhidrato de bupropion desde el dispositivo actt’ian cooperativamente para
presentar una velocidad de liberación in vitro tal que despuØs de 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de
35 aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆs de aproximadamente80% en peso de la sal bromhidrato de bupropion. En al

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menos una realización, el perfil de liberación in vitro de la sal bromhidrato de bupropion
es tal que despuØs de aproximadamente 2 horas, se libera no mÆs deaproximadamente
40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas, se libera a! menos
5 aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera al menos
aproximadamente 85%.

Ciertas realizaciones de la invención apuntan a formulaciones de brornhidrato de
bupropion de liberación sostenida para administrar una vez al dia que son bioequivalentes
10 segün las pautas de la FDA a WELLBUTRINTM ER o ZYBANTM/WELLBUTRINTM SR
cuando se administran una vez al dia a un sujeto que los necesita y donde la sal
bromhidrato de bupropion contenida es mÆs estable que unacantidad molar equivalente
de la sal clorhidrato de bupropion contenida en WELLBUTRINTM ER o ZYBANTM

0 cuando se exponen a condiciones similares, por ejemplo, cuando se almacenan durante
15 10, 13, 14, 20 o 24 dIas, 1, 2, 3, 4, 5, 6 o rnÆs meses, bajocondiciones de almacenamiento
acelerado (por ejemplo: a 40°C y 75% de humedad relativa). En al menos una
realización, la invenciOn abarca formulaciones de bromhidrato de bupropion de 174 mg,
348 mg y 522 mg que son bioequivalentes a las formulaciones de clorhidrato de
bupropion.
20

Al menos una realización apunta a formulaciones tópicas que contienen bromhidrato de bupropion que se pueden administrar tOpicamente por ejemplo, por via transrnucosa o transdØrrnica. Particularmente, la al menos una realización abarca geles y dispositivos de adrninistración tipo parches que pueden comprender otro principio activo como nicotina.

 25

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Al menos una realizaciOn apunta a composiciones inhalables de administración pulmonar
que contienen bromhidrato de bupropion que se pueden administrar por via pulmonar a
un sujeto que las necesita. Estas composiciones se pueden producir de acuerdo con la tecnologia del aerosol conocida en el area.

Al menos una realización apunta a composiciones inyectables que comprenden una cantidad eficaz de bromhidrato de bupropion y un vehIculo o excipiente
farmacØuticamente aceptable.

35 Al menos una realización apunta a un mØtodo para tratar una afección que comprende
administrar cualquiera de las formas farmacØuticas osmOticas descritas antes a un paciente que necesita dicha administración una vez al dia.

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Al menos una realización apunta a un mØtodo para administrar una sal bromhidrato de bupropion al aparato digestivo de un ser humano para el tratamiento o el manejo de una afecciOn, donde el mØtodo comprende: (a) ingresar oralmente en el ser humano una forma
5 farmacØutica de liberación modificada que comprende una sal bromhidrato de bupropion,
donde la forma farmacØutica de liberación modificada comprende una forma de administración osmOtica, y (b) administrar la sal bromhidrato de bupropion desde la
forma farmacØutica osmótica en una dosis que dØ una respuesta terapØutica para producir
el tratamiento o manejo de la afección de modo que la forma farmacØutica osmOtica
10 presente una velocidad de liberación in vitro tal que despuØs de 2 horas, se libera de
aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
15 en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se
libera mÆs de aproximadamente80% en peso de la sal bromhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de la sal bromhidrato de bupropion
es tal que despuØs de aproximadamente 2 horas, se libera no mÆsde aproximadamente
40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a
20 aproximadamente 75%, despuØs de aproximadamente 8 horas, se libera al menos
aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera al menos aproximadamente 85%.

Al menos una realización apunta a un mØtodo para administrar una sal bromhidrato de
1025 bupropion al aparato digestivo de un ser humano para el tratamiento o el manejo de una
afección, donde el mØtodo comprende: (a) ingresar oratmente en el ser humano una forma farmacØutica de liberación modificada que comprende un nücleo y una membrana que
rodea dicho nücleo, donde dicho niicleo comprende una sal bromhidrato de bupropion y opcionalmente un medio para dispensar forzadamente la sal bromhidrato de bupropion
30 desde el dispositivo, donde dicha membrana comprende al menos un medio para la salida
de la sal bromhidrato de bupropion desde la forma farmacØutica y (b) administrar la sal bromhidrato de bupropion desde la forma farmacØutica que Se formula de forma tal que cuando la forma farmacØutica estÆ en un medio acuoso, la sal bromhidratode bupropion
y opcionalmente el medio para dispensar forzadamente la sal bromhidrato de bupropion y
35 el al menos un medio para la salida de la sal bromhidrato de bupropion actüan
cooperativarnerite para presentar una velocidad de liberación in vitro tal que despuØs de 2 horas, se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal

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bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuds de
5 aproximadamente 16 horas, se libera mªs de aproximadamente 80% en peso de la sal
bromhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de
la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas, se libera
no rnÆs de aproximadamente40%, despuds de aproximadamente 4 horas, se libera de aproximadamente 40% a aproximadamente, 75%, despuØs de aproximadamente 8 horas,
10 se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 horas, se
libera al menos aproximadamente 85%.

Al menos una realización apunta a un mØtodo para administrar una sal bromhidrato de bupropion al aparato digstivo de un ser hurnano para el tratamiento o el xnanejo de una
15 afección, donde el mØtodo comprende: (a) ingresar oralmente en el ser humano una forma
farmacØutica de liberaeión modificada que comprende un nücleo y una membrana que
rodea dicho nücleo, donde dicho nücleo comprende una sal bromhidrato de bupropion, un medio para aumentar la presión hidrostÆtica dentro del nücleo y opcionalmente un medio
para dispensar forzadamente la sal bromhidrato de bupropion desde el dispositivo, donde
20 dicha membrana comprende al menos un medio para la salida de la sal brornhidrato de
bupropion desde la forma farmacØutica y (b) administrar la sal bromhidrato de bupropion desde la forma farmacdutica que se formula de forma tal que cuando la forma
farmacØutica estÆ en unmedio acuoso, la sal bromhidrato de bupropion, el medio para aurnentar la presión hidrostÆtica dentro del nücieo y opcionalrnente el medio para
25 dispensar forzadamente la sal bronihidrato de bupropion y el al menos un medio para la
salida de la sal bromhidrato de bupropion actiian cooperativamente para presentar una velocidad de liberación in vitro tal que despuØs de 2 horas, se libera de aproximadamente
0% a aproximadamente 20% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45%
30 en peso de la sal bromhidrato de bupropion, despuds de aproximadamente 8 horas, se
libera de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato
de bupropion y despuds de aproximadamente 16 horas, se libera rnÆs de
aproximadamente 80% en peso de!a sal bromhidrato de bupropion. En al menos una realización, el perifi de liberación in vitro de la sal bromhidrato de bupropion es tal que
35 despuØs de aproximadamente 2 horas, se libera no mÆs deaproximadamente 40%,
despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a aproximadamente 75%, despues de aproximadamente 8 horas, se libera a! menos

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aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera al menos aproximadamente 85%.

En al menos otra realizaciOn, la forma farmacdutica osmótica comprende ademÆs un
5 recubrimiento de liberaciOn inmediata para la liberación inmediata de la sal bromhidrato
de bupropion desde el recubrimiento de liberación inmediata. En realizaciones que comprenden el recubrimiento de liberación inmediata, la forma farmacØutica osmOtica presenta una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas
se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato
10 de bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a
aproximadamente 45% en peso de la Sal bromhidrato de bupropion, despuds de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, Se
IS libera mÆs de aproximadamente80% en peso de la sal bromhidrato de bupropion. En a!
15 menos una realización, el perfil de liberación in vitro de la sal bromhidrato de bupropion
es tal que despuØs de aproximadamente 2 horas, se libera no mÆsde aproximadamente
40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas, se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera al menos
20 aproximadamente 85%.

En al menos otra realizaciOn, la forma farmacØutica osmótica comprende un
recubrimiento inerte soluble en agua que cubre la membrana semipermeable o
recubrimiento. Este recubrimiento inerte soluble en agua puede ser impermeable en un
 5 primer ifquido extenjo, al mismo tiempo que es soluble en un segundo lIquido externo.
En realizaciones que comprenden el recubrimiento inerte soluble en agua, la forma farmacØutica osmótica presenta una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en
peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 4 horas se libera
30 de aproximadamente 15% a aproximadamente 45% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90% en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆsde aproximadamente 80% en peso de la sal bromhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de
35 la sal bromhidrato de bupropion es tal que despuØs de aproximadamente 2 horas, se libera
no mÆs deaproximadamente 40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a aproximadamente 75%, despuºs de aproximadamente 8 horas,
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se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera al menos aproximadamente 85%.

En al menos otra realización, las formas farmacØuticas osrnOticas comprenden adernªs un
5 subrecubrirniento osmótico. En ciertas realizaciones que comprenden el
subrecubrirniento osmótico, la forma farmacØutica osmótica presenta una velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a
10 aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de
aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera mÆs de aproximadamente80% en peso de la sal bromhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de la sal bromhidrato de bupropion
15 es tal que despuØs de aproximadamente 2 horas, se libera no mÆsde aproximadamente
40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a aproximadamente 75%, despuØs de aproximadamente 8 horas, se libera al menos aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera al menos aproximadamente 85%.
20

En al menos otra realización, las formas farmacØuticas osmóticas comprenden ademÆsun recubrirniento de liberación controlada. El recubrimiento de liberación controlada de la forma farmacØutica osmOtica puede, por ejemplo, controlar, extender y/o retardar la liberacjón de la sal bromhidrato de bupropion. En ciertas realizaciones que comprenden
25 el recubrimiento de liberación controlada, la forma farrnacØutica osmótica presenta una
velocidad de liberación in vitro tal que despuØs de aproximadamente 2 horas se libera de aproximadamente 0% a aproximadamente 20% en peso de la sal bronihidrato de
bupropion, despuØs de aproximadamente 4 horas se libera de aproximadamente 15% a aproximadamente 45% en peso de la sal bronthidrato de bupropion, despuØs de
30 aproximadamente 8 horas, se libera de aproximadamente 40% a aproximadamente 90%
en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16 horas, se libera rnas de aproximadamente 80% en peso de la sal brornhidrato de bupropion. En al menos una realización, el perfil de liberación in vitro de la sal bromhidrato de bupropion
es tal que despues de aproximadamente 2 horas, se libera no rnªs de aproximadamente
35 40%, despuØs de aproximadamente 4 horas, se libera de aproximadamente 40% a
aproximadamente 75%, despuØs de aproximadamente 8 horas, se libera al menos

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aproximadamente 75%, y despuØs de aproximadamente 16 horas, se libera at menos aproximadamente 85%.

En at menos una realizaciOn, el recubrimiento de liberación controlada de la forma farmacØutica osmótica comprende un material que es soluble en los jugos intestinales o erosionabie por dichos jugos, fundamentaimente los lIquidos de pH neutro o bÆsico de los lIquidos que tienen un pH superior at del lIquido gÆstrico pero en sumayor parte
insolubles en losjugos gÆstricos oliquidos Æcidos.

10 En at menos una realización, el recubrimiento de liberaeión controlada de la forma
farmacØutiea osmótica comprende al menos un polimero formador de pelicula, insoluble
en agua y permeable at agua y at menos un polimero soluble en agua.

En at menos una realización, el recubrimiento de liberaeión controlada de la forma
15 farmacØutica osmótica comprende at menos un polimero formador de pelicula, insoluble
en agua y permeable al agua y at menos un polimero soluble en agua y opcionalrnente at menos un plastificante.

En at menos una realización, el recubrimiento de iiberación controlada de la forma
20 farrnacØutiea osmótica comprende at menos un polimero formador de pelicula, insoluble
en agua y permeable at agua, at menos un polimero soluble en agua y at menos un medio
para la salida de la sal bromhidrato de bupropion desde el nücleo de la forma
farmacØutica osmótica.

1025 En at menos una realizaciOn, el recubrimiento de liberación controlada de la forma
farmacØutica osmótica comprende at menos un polimero formador de pelicula, insoluble
en agua y permeable at agua, at menos un polimero, soluble en agua y at menos un
pasadizo.

30 En at menos una realización, ci recubrimiento de liberaciOn controlada de la forma
farmacØutica osmótica comprende at menos un polimero formador de pelicula, insoluble
en agua y permeable at agua, at menos un polimero soluble en agua y at menos un piastificante.

35 En at menos una rea!ización, el recubrimiento de iiberación controlada de la forma
farmacØutica osmótica comprende at menos un polimero formador de pelicula, insoluble
en agua y permeable at agua, at menos un polimero soluble en agua, opcionaimente at

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menos un plastificante y al menos un medic para la salida de la sal bromhidrato de bupropion desde el nücleo de la forma farmacØutica osmótica.

En al menos una realización, el recubrimiento de liberación controlada de la forma
5 farmaeØutica osmótica comprende al menos un polimero formador de peilcula, insoluble
en agua y permeable al agua, al menos un polimero soluble en agua opcionalmente al
menos un plastificante y al menos un pasadizo.

En al menos una realizaciOn, el recubrimiento de liberación controlada de la forma
10 farrnacØutica osmótica comprende una dispersion acuosa de un copolimero de un ester
neutro sin ningün grupo funcional; un poliglicol con un punto de fusiOn mayor de 55°C aproximadamente, uno omÆs excipientesfarrnacØutieaxnente aceptables y opcionalmente
. al menos un rnedio para la salida de la sal bromhidrato de bupropion desde el nücleo de la
forma farmacØutica osmótica. Este recubrimiento de liberación controlada se cura a una
15 temperatura al menos mayor o igual que el punto de fusion del poliglicol.

En al menos otra realizaciOn, el recubrimiento de liberaciOn controlada de la forma
farmacØutica osmOtica comprende un polimero entØrico.

20 En algunas realizaciones la membrana o pared es permeable al pasaje de medics acuosos
pero no al pasaje de la sal bromhidrato de bupropion presente en el nücleo. La membrana puede ser, por ejemplo, una membrana semipermeable o una membrana asimØtrica, que puede ser permeable, semipermeable, perforada o no perforada y puede administrar la sal bromhidrato de bupropion mediante bombeo osmótico o los mecanismos coinbinados de
25 difusión y bombeo osmOtico. De preferencia, la integridad estructural de dichas
membranas permanece prÆcticamenteintacta durante el periodo de administraciOn de la
sal bromhidrato de bupropion. Por "prÆcticamenteintacta" se entiende que la propiedad semipermeable de la membrana no estÆcomprometida durante el perlodo de
administraciOn de la sal brornhidrato de bupropion.

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La membrana semipermeable de la forma farmacØutica osmótica de ciertas realizaciones comprende al menos un excipiente farmacØuticarnente aceptable, al menos un polimero, cera o combmaciOn de los mismos, aunque se pueden utilizar materiales inorgÆnicos apropiadamente titulados como cerÆmicas,metales o vidrio. Cuando la membrana
35 semipermeable comprende al menos un polimero, de preferencia, el peso molecular de al
menos un polimero o combinación de polIrneros es tal que el polimero o combinaciOn de polImeros es sólido a temperatura de usc, es decir, tanto in vitro come in vivo.

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En ciertas realizaciones, el al menos un polimero incluido en la membrana
semipermeable de la forma farmacØutica osmótica puede ser tin ester de celulosa, como
por ejemplo, acetato de celulosa, acetato acetoacetato de celulosa, acetato benzoato de
5 celulosa, acetato butilsulfonato de celulosa, acetato butirato de celulosa, acetato butirato
sulfato de celulosa, acetato butirato valerato de celulosa, acetato caprato de celulosa,
acetato caproato de celulosa, acetato caprilato de celulosa, acetato
carboximetoxipropionato de celulosa, acetato cloroacetato de celulosa, acetato dimetaminoacetato de celulosa, acetato dimetilaminoacetato de celulosa, acetato
10 dimetilsulfarnato de celulosa, acetato dipalmitato de celulosa, acetato dipropilsulfamato
de celulosa, acetato etoxiacetato de celulosa, acetato etilcarbamato de celulosa, acetato etilcarbonato de celulosa, acetato etiloxalato de celulosa, acetato furoato de celulosa,
acetato heptanoato de celulosa, acetato heptilato de celulosa, acetato isobutirato de
celulosa, acetato laurato de celulosa, acetato metacrilato de celulosa, acetato
15 metoxiacetato de celulosa, acetato metilcarbamato de celulosa, acetato metilsulfonato de
celulosa, acetato miristato de celulosa, acetato octanoato de celulosa, acetato palmitato de celulosa, acetato ftalato de celulosa, acetato propionato de celulosa, acetato propionato sulfato de celulosa, acetato propionato valerato de celulosa, acetato p-toluensulfonato de celulosa, acetato succinato de celulosa, acetato sulfato de celulosa, acetato trimelitato de
20 celulosa, acetato tripropionato de celulosa, acetato valerato de celulosa, benzoato de
celulosa, butirato naftilato de celulosa, butirato de celulosa, clorobenzoato de celulosa, cianoacetatos de celulosa, dicaprilato de celulosa, dioctanoato de celulosa, dipentariato de celulosa, dipentanlato de celulosa, formiato de celulosa, metacrilatos de celulosa, metoxibeuzoato de celulosa, nitrato de celulosa, nitrobenzoato de celulosa, fosfato de
1025 celulosa (sal sódica), fosfinatos de celulosa, fosfitos de celulosa, fosfonatos de celulosa,
propionato de celulosa, propionato crotonato de celulosa, propionato isobutirato de
celulosa, propionato succinato de celulosa, estearato de celulosa, sulfato de celulosa (sal
sódica), triacetato de celulosa, tricaprilato de celulosa, triformiato de celulosa,
triheptanoato de celulosa, triheptilato de celulosa, trilaurato de celulosa, trimiristato de
30 celulosa, trinitrato de celulosa, trioctanoato de celulosa, tripalmitato de celulosa,
tripropionato de celulosa, trisuccinato de celulosa, trivalerato de celulosa, valerato
palmitato de celulosa; un Cter de celulosa, como por ejemplo, 2-cianoetilcelulosa, 2-hidroxibutil metil celulosa, 2-hidroxietilcelulosa, 2-hidroxietil etil celulosa, 2-hidroxietil metil celulosa, 2-hidroxipropilcelulosa, 2-hidroxipropil metil celulosa, acetato de
35 dimetoxietilcelulosa, etil 2-hidroxiletil celulosa, etilcelulosa, sulfato de etilcelulosa,
dimetilsulfamato de etilcelulosa, metilcelulosa, acetato de metilcelulosa, metil cianoetil celulosa, carboxirnetil 2-hidroxietilcelulosa sódica, carboximetilcelulosa sódica; una

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polisulfona, como pot ejemplo, poliØtersulfonas; un policarbonato; un poliuretano; un acetato de polivinilo; tin alcohol polivinlilco; un polister; un polialqueno como
polietileno, copoilmero de etileno y alcohol vinilico, polipropileno, poli(1,2-dimetil-1-butenileno), poli(1 -bromo- 1 -butenileno), poli(1 -buteno), poli(1 -cloro- 1 -butenileno),
5 poli(1 -decil- 1 -butenileno), poli(1 -hexano), poli(1 -isopropil- 1 -butenileno), poli(1 -
penteno), poli(3-vinilpireno), poli(4-metoxil- 1 -butenileno), poli(etileno-co-metilestireno), cloruro de polivinilo, poli(etileno-co-tetrafluoroetileno), poli(tereftalato de etileno), poli(dodecafluorobutoxiletileno), poli(hexafluoroprolileno), poli(hexiloxietileno), poli(isobuteno), poli(isobuteno-co-isopreno), poli(isopreno), poli-butadieno,
10 poli[(pentafluoroetil)etileno], poli[2-etilhexiloxi)etilenoj, poli(butiletileno),
poli(tercbutiletileno), poli(cilclobexiletileno), poli[(ciclohexilmetil)etilenoj, poli(ciclopentiletileno), poli(deciletileno), poli-(dodeciletileno), poli(neopentiletileno), poli(propiletileno); un poliestireno, como por ejemplo, poli(2,4-dimetilestireno), poli(3-metilestireno), poli(4-metoxiestireno), poli(4-metoxiestireno-stat-estireno), poli(4-
15 metilestireno), poli(isopentilestireno), poli(isopropilestireno), Østeres polivinIlicos o
ºteres polivinIlicos, como por ejemplo, poli(benzoiletileno), poli(butoxietileno), poli(cloropreno), poli(ciclohexiloxietileno), poli(deciloxietileno), poli(dicloroetileno), poli(difluoroetileno), poli(aeetato de vinilo), poli(viniltrimetilestireno; un polisiloxano,
como por ejemplo, poli(dimetilsiloxano); un derivado de ÆcidopoliacrIlico, como por
20 ejemplo, poliacrilatos, polimetil metacrilato, poli Østeres de aiquilos superiores de (Æcido
acrilico), poli(metacrilato de etilo), poli(metacrilato de hexadecilo-co-metacrilato de
metilo), poli-(acrilato de metilo-co-estireno), poli(metacrilato de n-butilo), poli(acrilato
de n-butilo), poli(acrilato de ciclododecilo), poli(acrilato de bencilo), poli(acrilato de
butilo), poli(acrilato de seebutilo), poli(acrilato de hexilo), poli(acrilato de octilo),
25 poli(acrilato de decilo), poli(acrilato de dodecilo), poli(acrilato de 2-metilbutilo),
poli(metacrilato de adamantilo), poli(metacrilato de bencilo), poli(metacrilato de butilo), poli(metacrilato de 2-etilhexilo), poli(metacrilato de octilo), resinas acrIlicas; una
poliamida, como por ejemplo, poli(iminoadipoiliminododecametileno), poli(iminoadipoiliminohexametileno), poliØteres, como por ejemplo, poli(octiloxietileno),
30 poli(oxifeniletileno), poli(oxipropileno), poli(pentiloxietileno), poli(fenoxiestireno),
poli(secbutroxiletileno), poli(terc-butoxietileno); y sus combinaciones.

En al menos una realización, la al menos una cera incluida en la membrana
semipermeable de la forma farmacØutiea osmótica puede ser, por ejemplo, cera de
35 insectos o animales, como por ejemplo, cera de China, cera de abeja, esperma de ballena,
grasas y cera de lana; ceras vegetales, como por ejemplo, cera de hoj a de bambü, cera de candelilla, cera carnauba, cera de Japón, cera de ouricuri, cera de j oj oba, cera del Ærbolde

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la cera, cera de abeto Douglas, cera de algodón, cera de arÆndano rojo,cera de cape berry, cera de cascara de arroz, cera de ricino, cera de maiz indio, aceites vegetales hidrogenados (por ejemplo, de ricino, palma, semilla de algodon, soja), cera de grano de sorgo, cera de musgo espafiol, cera de cafia de azücar, cera de caranda, cera blanqueada,
cera de esparto, cera de lino, cera de Madagascar, cera de cascara de naranja, cera de laca, cera de cÆfiamoy cera de arroz; ceras minerales, como por ejemplo, cera de Montan,
ceras de turba, cera de petróleo, ceresina, ozocerita, cera microcristalina y parafinas;
ceras sintØticas, como por ejemplo, cera de polietileno, cera de Fischer-Tropsch, ceras de hidrocarburos modificados qulmicamente, cera de Østeres de cetilo; y sus combinaciones.

10

En al menos una realizaeión, la membrana semipermeable de la forma farmaeØutica
osmótica puede contener una combinación de al menos un poilmero, cera o
combinaciones de Østos y opcionalmente al menos un excipiente.

15 En realizaciones en las que la sal bromhidrato de bupropion se libera a travØs de la
membrana o pared de forma controlada mediante los mecanismos combinados de
difusión y bombeo osmOtico, la membrana o pared puede contener al menos uno de los poilmeros y/o ceras antes descritos o una combinaciOn de pollmeros, como por ejemplo, Østeres de celulosa, copolImeros de sales de metacrilato y en forma opcional un
20 plastificante.

Las sales de copolimero de poli(metacrilato) usadas en la fabricación de la membrana
para la forma farmacØutiea osmOtica pueden ser, por ejemplo, insolubles en agua y en
liquidos digestivos, pero son permeables en diferentes grados. Algunos ejemplos de
025 dichos copolImeros son copolImero RL de poli(metacrilato de amonio) (EUDRAGITfi
RL), copolfmero de poli(metacrilato de amonio) (tipo A-USP/NF), copolfmero (RL-JSPI)
de poli(metacrilato de aminoalquilo), y copoilmero de (acrilato de etilo)-(metacrilato de metilo)-[etilmetacrilato de (trimetilamonio)] (1:2:0,2), PM 150.000. Otros ejemplos de
dichos copolimeros incluyen EUDRAGITfi RS 100: polImero sOlido, EUDRAGITfi RL
30 12.5: solución al 12,5% en disolvente, EUDRAGITfi RL 30 D: dispersiOn acuosa al
30%, y otros productos equivalentes. TambiØn se pueden usar los siguientes copolImeros
de poli(metacrilato de amonio): copoilmero RS de metacrilato de amonio (EUDRAGITfi RS), copolImero de poli(metacrilato de amonio) (tipo B-USP/NF), copoilmero (RSL-JSP
I) de poli(metacrilato de aminoalqui!o), copolImero de (aerilato de etilo)-(metacrilato de
35 metilo)-[etilmetacrilato de (trimetilamonio)] (1:2:0,1), PM 150.000. Los polImeros
especIficos incluyen: EUDRAGITfiRS 100: po!lmero sOJido, EUDRAGITfi RS 12.5: solución al 12,5% en disolvente, EUDRAGITfi RS 30 D: dispersion acuosa a! 30%, y

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otros productos equivalentes. El RL es muy permeable al agua mientras que
EUDRAGITfi RS es apenas permeable a! agua. Al emplear mezelas de EUDRAGITfi
RL y EUDRAGITfi RS, se pueden preparar membranas que tengan el grado deseado de
permeabilidad para lograr las velocidades de disolución in vitro y los parªmetros
farmacocinØticos in vivo.

El uso de plastificantes es opcional pero puede estar incluido en las formas osmóticas de
ciertas realizaciones para modificar las propiedades y las caracteristicas de los polimeros usados en los recubrimientos o el nücieo de las formas osmOticas para el procesamiento
10 conveniente durante la fabricación de los recubrimientos y/o del nücleo de las formas
farrnacØutica osm.ótica, si fuera necesario. El tØrmino "plastificante" como se usa aqul,
incluye a todos los compuestos capaces de plastificar o ablandar un polImero o
. aglutinante usado en la invención. Una vez que se preparO el recubrimiento o membrana,
ciertos plastificantes pueden actuar para aumentar la hidrofilicidad del o de los
15 recubrimientos y/o del nücleo de la forma farmacØutica osrnótica en el ambiente de uso.
Durante la fabricación del recubrimiento, el plastificante puede disminuir la temperatura
de fusion o la temperatura de transición vitrea (temperatura del punto de ablandamiento)
del polImero o aglutinante. Los plastificantes, como los PEG de bajo peso molecular
pueden incluirse con un poilmero y asi disminuir su punto transición vitrea o de punto de
20 ablandamiento. Los plastificantes tambiØn pueden reducir la viseosidad de un poilmero.
El plastificante puede impartir algunas propiedades fisicas particu!armente ventajosas al dispositivo osmótico de la invención.

Los plastificantes utilizados en la forma farmacØutica osrnótica de algunas realizaciones
25 de la invención pueden comprender polimeros de bajo peso molecular, oligomeros,
copolImeros, aceites, molØculas orgnicas pequefias, polioles de bajo peso molecular que tienen hidroxilos alifÆticos,plastificantes del tipo ester, Øteres de glicol,
poli(propilenglicol), polimeros multibloque, polimeros de bloque ünico, poli(etilenglicol)
de bajo peso molecular, plastificantes del tipo ester de citrato, triacetina, propilenglicol,
30 glicerina, etilenglicol, 1,2-butilenglicol, 2,3 -butilenglicol, estirenglicol, dietilenglicol,
trietilenglicol, tetraetilenglicol, y otros compuestos de poli(etilen)glicol, Øter monoisopropIlico de monopropilenglicol, Øter monoetilico de propilenglicol, Cter monoetIlico de dietilenglicol, lactato de sorbitol, lactato de etilo, glicolato de etilo, dibutjlsebacato, acetiltributjlacetato, citrato de trietilo, citrato de trietilacetilo, citrato de
35 tributilo, glicolato de alilo y mezelas de los mismos. EstÆ contempladoy dentro del
alcance de la invenciOn, que se puede usar una combinación de plastificantes en la
presente formulación. Los plastificantes a base de PEG estÆndisponibles en el mercado

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o se pueden preparar por diversos mØtodos, çomo se describe en Poly(ethylene glycol) Chemistry: Biotecimical and Biomedical Applications (J.M. Harris, Ed.; Plenum Press,
NY). Una vez que se fabrica la forma farmacØutica osmótica, ciertos plastificantes
pueden actuar para aumentar la hidrofilicidad del o los recubrimientos y/o del nücleo de
5 la forma farmacØutica osmOtica en el ambiente de uso, sea in vitro o in vivo.
Consecuentemente, algunos plastificantes pueden actuar como mejoradores del flujo.

La relaciOn de Østeres de celulosa: copolirneros de sales de metacrilato de las formas farmacØuticas osmóticas puede ser, por ejemplo, de aproximadamente 1% a
10 aproximadamente 99% del ester de celulosa en peso: aproximadamente 0,5% a
aproximadamente 84% de los copolimeros de la sal metacrilato en peso:
aproximadamente 0,5% a aproximadamente 15% del plastificante en peso incluyendo
todos los valores y rangos entre ellos. El peso porcentual total de todos los componentes
que formari la pared es de 100%.
15

Aparte de las membranas semipermeables de la forma farmacØuticas osmóticas descrita
antes, tambiØn se pueden usar membranas asimØtricas para rodear ci nücleo de una forma famiacØutica osmOtica para la liberaciOn controlada de la sal bromhidrato de bupropion
para proporcionar las velocidades de liberaciOn in vitro descritas antes y los parÆmetros
20 fannacocinØticos terapØuticamente beneficiosos in vivo para ci tratamiento o ci manejo
de una afección. Dichas membranas asimØtricas pueden ser permeables, semipermeables, perforadas o no perforadas y pueden liberar la sal bromhidrato de bupropion mediante
bombeo osmótico, difusión o los mecanismos combinados de diftisión y bombeo
osmótico. Se conoce la fabricaciOn y uso de las membranas asimØtricas para la liberaciOn
1025 controlada de un fÆrmaco activoa travØs de una o mÆsmembranas asimØtricas por
Osmosis o por una combinación de bombeo de difusión osmOtica.

En aigunas realizaciones de la forma farmacØutica osmOtica, la membrana semipermeable
puede contener ademÆs un mejoradordel flujo o agente generador de canales. Los
30 "agentes mejoradores del flujo" o "agentes generadores de canales" son materiales que
actüan aumentando ci volumen de liquido embebido en el nücieo para permitir que la
forma farmacØutica osmótica dispense prÆcticamente toda la sal brornhidrato de
bupropion a travØs de al menos un pasadizo en la membrana semipermeable, por Osmosis
o por Osmosis y difusión a travØs de la membrana semipermeable. El agente mejorador
35 del flujo se disuelve para formar caminos en la membrana semipermeable para que el
lIquido ingrese en ci nücleo y disuelva la sal bromhidrato de bupropion en el nücleo junto
con el osmoagente, si hay uno presente, pero no permita la salida de la sal bromhidrato de
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bupropion. El agente mejorador del flujo puede ser cualquier material soluble en agua o un material entØrico que permita un aumento en el volumen de lIquido embebido en el nücleo pero que no permita la salida de la sal de bupropion. Dichos materiales pueden ser, por ejemplo, cloruro de sodio, cloruro de potasio, sacarosa, sorbitol, manitol, polietilenglicol, propilenglicol, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, ftalato
de hidroxipropil metilcelulosa, acetato flalato de celulosa, alcoholes polivinilicos, copoilmeros metacrilicos y sus combinaciones. Algunos plastificantes pueden actuar
como inejoradores del flujo aumentando la hidrofilicidad de la membrana semipermeable
y/o el nücleo de la forma farmacØutica osrnOtica. Los mejoradores del flujo o agentes
10 formadores de canales tambiØn pueden actuar como un medio para la salida de la sal
bromhidrato de bupropion desde el nücleo si el agente mejorador del flujo o formador de canales se usa en cantidad suficiente.

La expresión ’pasadizo" como se usa aqul comprende medios y mØtodos adecuados para
15 la liberación medida de la sal bromhidrato de bupropion desde el nücleo de la forma
farmacØutica osmótica. Los medios para la salida de la sal bromhidrato de bupropion comprenden al menos un pasadizo, incluidos un orificio, perforación, abertura, poro, elemento poroso, fibra hueca, tubo capilar, recubrimiento poroso o elemento poroso que aseguren la liberación osmótica controlada de la sal bromhidrato de bupropion. El
20 medio para la salida puede ser lineal o tortuoso. Los medios para la salida incluyen un
area debilitada de la membrana semipermeable o un material que sea erosionado o
lixiviado de la pared en un ambiente liquido de uso para producir al menos un pasadizo unidirnensional. El medio para la salida de la sal bromhidrato de bupropion puede
incluir cualquier material lixiviable, que cuando se lixivia de la membrana
25 semipermeable forma.un pasadizo adecuado para la salida de la sal bromhidrato de
bupropion desde el nücleo de la forma de dosificación farmacØutica. Dichos materiales lixiviables pueden contener, por ejemplo, un Æcido poli(glicolico)o un polimero del Æcido poli(lÆctico)lixiaviables en la membrana semipermeable, un filamento gelatinoso,
poli(vinil alcohol), polisacÆridoslixiviables, sales, óxidos, sorbitol, sacarosa o mezelas de
30 los mismos. El medio para la salida tambiØn puede contener un mejorador del flujo o
agente formador de canales si estÆ presenteen cantidad suficiente. El medio para la
salida posee dirnensiones de liberación controlada, como redonda, triangular, cuadrada y eliptica, para la liberación regulada de la sal brornhidrato de bupropion desde la forma de dosificación. Las dimensiones del medio para la salida de la sal brornhidrato de
35 bupropion son las adecuadas para permitir que la sal bromhidrato de bupropion pase a
travØs del medio para la salida. La forma de dosificaciOn se puede elaborar con uno o

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mÆs medios para Lasalida en una relación de separación espacial en una superficie iinica
o en mÆs de unasuperficie de La pared.

La expresión "axnbiente lIquid& denota un liquido acuoso o biológico como en un
5 paciente humano, incluido el tracto gastrointestinal. El medio para La salida puede ser
preformado, por ejemplo, por medios mecÆnicos despuØs de que Lamembrana semipermeable se aplica al ncleo de la forma farmacØutica osmótica, tal como por
ejemplo, mediante perforación mecÆnica, perforación con laser, o usando una saliente del tamafio adecuado en el interior del punzón de comprimidos para formar ci medio para la
10 salida de La sal bromhidrato de bupropion, como por ejemplo, una punta cilIndrica o
cónica trunca que forme parte integral de la superficie interior del punzón superior de un
punzón usado para formar la forma farmacØutica osmótica. Como alternativa, ci medio
para la salida de la sal brornhidrato de bupropion se puede formar incorporando un
40 material lixiviable o un agente formador de poros en la composición semipermeable antes
15 de aplicar la membrana semipermeable al nücleo de la forma farmacØutica osmótica. El
medio para la salida de la sal bromhidrato de bupropion puede comprender una
combinaciOn de los diferentes medios para la salida descritos antes. La forma
farmacØutica osmótica puede contener mÆs de unmedio para la salida de la sal
bromhidrato de bupropion incluidos dos, tres, cuatro, cinco, seis, siete, ocho, nueve, diez
20 o mÆs medios para lasalida y se pueden formar en cuaiquier lugar de la forma
farmacØutica osmótica. Se describen las diversas posiciones para ci medio de salida. El
tipo, nümero y dimensiones del medio de salida para la sal bromhidrato de bupropion
son tales que la forma de dosificación exhibe las velocidades de liberación in vitro
deseadas descritas en este documento y pueden ser deterniinados mediante experimentos
de rutina a cargo de expertos en las tØcnicas de administración farmacØutica. Se conocen
el medio y ci equipo para la formaciOn del medio de salida.

El dispositivo osmótico tajnbiØn puede contener un recubrimiento de control de la
liberación rodeando la membrana semipermeable que comprende un recubrimiento
30 entØrico o de liberación retardada que es soluble o erosionabie en los jugos intestinales,
fundamentalmente en los lfquidos de pH neutro o bÆsico de los lIquidos quetienen un pH mayor que ci del jugo gÆstrico, pero en su mayor parteinsoluble en jugos gÆstricoso
liquidos Æcidos. Se conoceuna ampiia variedad de otros materiales polimØricos que
poseen estas diversas propiedades de solubilidad. Entre esos otros materiales polimØricos
35 se incluyen, por ejemplo, acetato ftaiato de celulosa (CAP), acetato trimeletato de
celulosa (CAT), flalato de poli(acetato de vinilo) (PVAP), ftalato de hidroxipropilmetilcelulosa (HP), copolImero de poli(metacrilato acrilato de etilo) (1:1)

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(MA-EA), copoilmero de poli(rnetacrilato metacrilato de metilo) (1:1) (MA-MMA), copoilmero de poli(metacrilato metacrilato de metilo) (1:2), EUDRAGITfi L-30-D (MA-EA, 1:1), EUDRAGITfi L-100-55 (MA-BA, 1:1), acetato succinato de hidroxipropilmetilcelulosa (HPMCAS), COATERICfi (PYAP), AQUATERICfi (CAP), AQUACOATfi (HPMCAS) y sus combinaciones. El recubrimiento entØrico tambiØn
puede contener auxiliares de disoluciOn, modificadores de la estabilidad y potenciadores
de la bioabsorción.

En al menos una realización, el recubrimiento de liberaeión controlada de algunas formas
10 farmacØuticas osmóticas comprenden materiales como la hidroxipropilcelulosa, celulosa
microcristalina (pot ejemplo, MCC, AVICELTM), copolimero de (etileno acetato de
vinilo) (60:40) (EVAC), metacrilato de 2-hidroxietilo (HEMA), MMA, terpolirneros de HEMA: MMA:MA sintetizados en presencia de N,N’- bis(metacriloiloxietiloxicarbonilarnino)-azobenzeno, azopolimeros, sistema de liberación
15 controlada con recubrimiento entØrico (TIME CLOCKfi), pectinato de calcio y sus
mezelas.

Los polImeros para usar en el recubrimiento de liberación controlada de las formas farmacØuticas osmóticas de algunas realizaciones pueden ser, por ejemplo, materiales
20 entØricos que resisten la acción del 11 quido gÆstrico evitando la penetración a travØs de la
pared semipermeable mientras uno o mÆs delos materiales del nücleo de la forma de dosificaciOn se solubilizan en el intestino, permitiendo asI que comience la liberación de
la sal bromhidrato de bupropion del nücleo mediante bombeo osmótico de la forma
. farmacØutiea osmótica. Un material que se adapta a este tipo de requisitos puede set, pot
25 ejemplo, un copolImero de poli(vinilpirrolidona)-acetato de vinilo (por ejemplo,
KOLLIDONfi VA64), mezclado con estearato de rnagnesio y otros excipientes sirnilares.
El recubrimiento puede tambiØn comprender povidona (e.g. KOLLIDONfi K 30), e hidroxipropilmetilcelulosa (por ejemplo, METIIOCELfi E-15). Los materiales pueden prepararse en soluciones que tienen diferentes concentraciones del polImero segün la
30 viscosidad de la solución deseada. Por ejemplo, una solución acuosa a! 10% P/v de
KOLLIDONfi K 30 tiene una viscosidad de aproximadamente 5,5 a aproximadamente
8,5 cp a 20°C y una solución acuosa al 2% P/V de METHOCELfi E- 15 tiene una
viscosidad de aproximadamente 13 a aproximadamente 18 cp a 20°C.

35 El recubrimiento de liberación controlada de las formas farmacØuticas osrnóticas de
algunas realizaciones pueden comprender uno o mÆs materialesque no se disuelven, desintegran ni cambian su estructura integral en el estómago durante el perlodo durante el

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cual el comprimido reside en ci estómago, como un ejemplo elegido entre ci grupo de (a) queratina, queratina sandarac-told, salol (salicilato do fenilo), beta naftulbenzoato de salol
y acetotanino, salol con bÆlsamode Peru, salol con told, salol con goma mÆstica,salol y Æcido estØarico,y salol y goma laca; (b) un miembro elegido entre el grupo de protelna
5 formalizada, gelatina formalizada y gelatina formalizada reticulada y resinas de
intercambio; (c) un miembro elegido entre el grupo de ÆcidomirIstico-aceite de ricino hidrogenado-colesterol, ÆcidoesteÆrico-sebo de oveja,ÆcidoesteÆrico-bÆlsamode told, y Æcido esteÆrico-aceitede ricino; (d) un miembro elegido entre ci grupo de goma laca,
goma laca amoniacal, goma laca amoniacal-salol, goma laca-grasa de lana, goma laca-
10 acetilalcohol, goma laca-Æcido esteÆrico-bÆlsamode told, y goma laca estoarato de n-
butilo; (e) un miembro elegido entre el grupo de ÆcidoabiØtico, abietato de metilo,
bonzoina, bÆlsamo detold, sandarac, y goma mÆsticacon told y goma mÆsticacon acetilalcohol; (f) resinas acrIiicas representadas por poilmeros aniónicos sintetizados a

49 partir del Æcidometacrilico y ester metIlico del Æcidometacrilico, resinas acrIlicas
15 copo1imricas del Æcido metacrilicoy Æeidometacrilico y Østeres aiquflicos del Æcido
metacrilico, copoilmeros de ÆcidoalcacrIlico y Østeres alquIlicos del ÆcidoalcacrIlico,
resinas acrflicas tales como copolfmero de aminoetilmetacrilato de dimetilo-metacrilato
de butilo-motacrilato de metilo de peso molecular 150.000, copoilmero de Æcido metacrilico-metacrilato do metilo 50:50 de peso molecular 135.000, copolimero de Æcido
20 metacrilico-metacrilato do metilo 30:70 de P.M. 135.000, Æcidometacrilico-
aminoetilmetacrilato de dimetilo-acrilato do etilo de P.M. 750.000, Æcidometacrilico-
metacriiato de metilo-acrilato de etilo de P.M. 1.000.000, y acrilato do etilo-metacrilato
de metilo-acrilato do etilo de P.M. 550.000; y, (g) una composición entØrica elegida entre
ci grupo do acetilfialato de celulosa, diacetilfialato de celulosa, triacetilftalato de celulosa,
1025 acetato ftalato do celulosa, ftalato do hidroxipropil metilcelulosa, acetato ftalato, do
celulosa sOdica, ftalato do ester de celulosa, ftalato de Øter de celulosa, ftalato do
metilcelulosa, ftalato de Øster-Øter de celulosa, ftalato de hidroxipropil celulosa, sales
alcalinas de acetato ftalato do celulosa, sales aicalinotCrreas do acetato ftalato do celulosa,
sal de calcio do acetato ftalato de celulosa, sal de amonio do ftalato do
30 hidroxipropilmetilcelulosa, acetato hexahidroftalato de celulosa, hexahidroftalato de
hidroxipropilmetilcelulosa, acetato ftalato de polivinilo, ftalato do dietilo, ftalato do
dibutilo, ftalato de dialquilo en el cual ci alquilo comprende do 1 a 7 grupos aiquilo
lineales y ramificados, ftalatos de arilo y otros materiales conocidos por los tØcnicos con experiencia en el area. Las combinaciones de los mismos son factibles.

35

Por consiguiente, en al menos otra realización, ci recubrimiento do liberación controlada
do las formas farmacCuticas osmóticas do la presente invonción contiene un polimero

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formador de pelfcula insoluble en agua y permeable al agua, un poilmero soluble en agua
y opcionalmente un plastificante y/o un agente formador de poros. Los polinieros formadores de pelleula insolubles en agua y permeables al agua ütiles para la fabricación
del recubrimiento de liberación controlada pueden ser Øteres de celulosa, como por
5 ejemplo, etilcelulosas elegidas entre el grupo de etilcelulosa grado PR 100, etilcelulosa
grado PR 20, Østeres de celulosa, alcohol polivinilico y cualquiera de sus combinaciones.
Los polImeros solubles en agua ütiies para el recubrimiento de liberación controlada
pueden ser, por ejemplo, polivinilpirrolidona, hidroxipropilmetilcelulosa, hidroxipropilcelulosa y cualquiera de sus combinaciones.

10

El tØcnico eon experiencia apreciard que las velocidades de liberación in vitro deseadas descritas aqul para la sal bromhidrato de bupropion se pueden lograr controlando la permeabilidad y/o la cantidad del recubrimiento aplicado al nücleo de la forma
farmacØutica osmótica. La permeabilidad del recubrimiento de liberación controlada se
15 puede alterar variando la reiación entre poilmero formador de pelIcula insoluble en agua
y permeable al agua:po!Imero soluble en agua:plastificante opcionai y/o la cantidad de recubrimiento aplicada al nücleo de la forma farmacØutica osmOtica. Una liberación mÆs extendida se obtiene generalmente con una mayor cantidad de polimero formador de
pelIcula insoluble en agua y permeable al agua. La adiciOn de otros excipientes al nücieo
20 de la forma farmacØutica osmótica tambiØn puede alterar la permeabilidad del
recubrimiento, de liberación controlada. Por ejemplo, si ci nücico de la forma
farmacØutica osrnOtica contiene un polImero hinchable, la cantidad de plastificante del recubrimiento de iiberación controlada se puede aumentar para hacer que el
. recubrimiento sea mÆs flexible dadoque la presión ejereida en un recubrimiento menos
25 flexible por parte del poilmero hinchable podrIa romper el recubrimiento. AdemÆs, la
proporción del polImero insoluble en agua y permeable al agua y el polimero soluble en
agua tambiºn se puede alterar dependiendo de si se desea una disolución in vitro mÆs
rÆpidao n.Æs lenta.

30 En al menos otra realizaeión, ci recubrimiento de liberación controlada de la forma
farmaeØutica osmótica contiene una dispersion acuosa de un copoilmero de un ester
neutro sin ningün grupo funcional; un poliglicol con un panto de fusiOn mayor de 55°C, y uno o mas excipientes farmacØuticamente aceptables y se cura a una temperatura al
menos mayor o igual que el punto de fusion del poliglicol. Se conocen la fabricaciOn y el
35 uso de dichas formulaciones de recubrimiento. En resumen, EUDRAGITfi NE30D,
EUDRAGITfi NE401), o sus mezelas pueden constituir ejemplos de copolImeros de ester neutros sin ningün grupo funcional comprendidos en ci recubrimiento. Este

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recubrimiento puede contener agentes hidrófilos para promover la humectación del recubrimiento cuando estÆ encontacto con los fluidos gastrointestinales. Dichos agentes hidrófilos incluyen, por ejemplo, poilmeros hidrófflos solubles en agua como hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC) y sus combinaciones.
El poliglicol Se puede elegir, por ejemplo, entre el grupo de polietilenglicol 6000, polietilenglicol 8000, polietilenglicol 10000, polietilenglicol 20000, Poloxamer 188, Poloxamer 338, Poloxamer 407, óxidos de polietileno, Øteres aiqullicos de polioxietileno,
y estearatos de polioxietileno, y sus combinaciones. Este recubrimiento de liberación controlada de la forma farmacºutica osmótiea puede contener ademÆs un agenteformador
10 de poros. En al menos una realización, el fonnador de poros es lo suficientemente
insoluble en la dispersion acuosa y lo suficientemente soluble en el ambiente de uso. Se conocen los mØtodos para la producción de dichos recubrimientos.

El recubrimiento de liberación controlada de ciertas realizaciones de la forma
15 farmacØutica osrnótica de ciertas realizaciones de la presente invención incluye al rnenos
un polImero en una cantidad suficiente para lograr una liberación controlada de la sal bromhidrato de bupropion. Otros ejemplos de polimeros que se pueden usar en el recubrimiento de liberación controlada de estas realizaciones incluyen acetato ftalato de celulosa, acetato trimaleato de celulosa, ftalato de hidroxipropilmetilcelulosa, acetato
20 ftalato de polivinilo, copolImeros de metacrilato de amonio como los comercializados
bajo la marca registrada EUDRAGITfi RS y RL, copolimeros de Æcido poliacrIlicoy poliacrilato y metacrilato como los comercializados bajo la marca registrada
EUDRAGITfi S y L, acetato de polivinil acetaldietilamino, acetato succinato de hidroxipropilmetilcelulosa, goma laca; hidrogeles y materiales que forman geles, como
925 polImeros carboxivinflicos, alginato de sodio, carmelosa de sodio, carmelosa de calcio,
carboximetil almidón sódico, alcohol polivinIlico, hidroxietilcelulosa, metilcelulosa,
gelatina, almidón y polImeros reticulados a base de celulosa en los que el grado de
reticulaciOn es bajo de modo de facilitar la adsorción de agua y la expansion de la matriz polimØrica, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona,
30 almidón reticulado, celulosa microcristalina, quitina, copolImero arninoacril-metacrilato
(EUDRAGITfi RS-PM), pullulan, colªgeno, caselna, agar, goma arÆbiga, carboximetilcelulosa de sodio, (poilmeros hidrófilos hinchables) poli(metacrilato de hidroxialquilo) (peso molecular de 5 k a 5.000 k), polivinilpirrolidona (peso molecular de
10 k a 360 k), hidrogeles aniOnicos y catiOnicos, alcohol polivinulico con bajo contenido
35 de acetato residual, una mezela hinchable de agar y carboximetilcelulosa, copolimeros de
anhidrido maleico y estireno, etileno, propileno o isobutileno, pectina (peso molecular 30
k a 300 k), polisacÆridoscomo agar, goma de acacia, goma karaya, goma tragacanto,

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alginas y goma guar, poliacrilarnidas, Oxidos de polietileno POLYOXfi (peso molecular
de 100 k a 5.000 k), polimeros de acrilato AQUAKEEPfi, diØsteres de poliglucano,
alcohol polivinilico y poli N-vinil-2-pirrolidona reticulados, glicolato de alrnidOn sOdico (por ejemplo, EXPLOTABfi); polimeros hidrófilos como los polisacÆridos,
5 metilcelulosa, carboxirnetilcelulosa de sodio o de calcio, hidroxipropilmetilcelulosa,
hidroxipropilcelulosa, hidroxietilcelulosa, nitrocelulosa, carboxirnetilcelulosa, Øteres de celulosa, óxidos de polietileno (por ejemplo, POLYOXfi), metil etil celulosa, etil hidroxietil celulosa, acetato de celulosa, butirato de celulosa, propionato de celulosa, gelatina, colªgeno, almidOn, maltodextrina, pullulan, polivinilpirrolidona, alcohol
10 polivinIlico, acetato de polivinilo, Østeres de Æcidos grasos de glicerol, poliacrilarnida,
ÆcidopoliacrIlico, copoilmeros de Æcido metacrIlico o Æcido metacrilico (porejemplo, EUDRAGITfi), otros derivados del Æcido acrIlico, Østeres de sorbitÆn,gomas naturales, lecitinas, pectina, alginatos, alginato de amonio, alginatos de sodio, calcio y potasio,
alginato de propilenglicol, agar y gomas como arÆbiga, karaya, de algarrobo,tragacanto,
15 carrageninas, guar, xantano, escieroglucano y sus mezcias y combinaciones. En al menos
una realización de la forma farmacØutica osmótica de la presente invención, el polimero
es una dispersion de acrilato como EUDRAGITfi NE30D, EUDRAGITfi NE40D, KOLLICOATfi SR 30D, SURELEASEfi o una mezela de Østos. El poilmero puede
estar presente en una cantidad desde aproximadamente 20% a aproximadamente 90% en
20 peso del recubrimiento de liberación controlada e incluye todos los valores y rangos
intennedios, dependiendo del perfil de liberación controlada deseado. Por ejemplo, en ciertas realizaciones de la forma farmacØutica osmótica, el poilmero estÆ presente en una cantidad entre aproximadamente 50% y aproximadamente 95%, en otras realizaciones
entre aproximadamente 60% y aproximadamente 90% y aun en otras realizaciones en
25 aproximadamente 75% del peso del recubrimiento de liberación controlada.

El recubrimiento de liberación controlada de ciertas realizaciones de la forma
farmacØutica osmótica de la presente invención tambiØn puede incluir uno o mÆs
excipientes farmacØuticarnente aceptables como lubricantes, ernulsionantes,
30 antiespumantes, plastificantes, disolventes y sirnilares.

Se pueden incluir lubricantes en el recubrimiento de liberación controlada de ciertas realizaciones de la forma farinacØutica osmótica de la presente invención para ayudar a reducir la fricción de las microparticulas recubiertas durante la fabricaciOn. Los
35 lubricantes que se pueden usar en el recubrimiento de liberación controlada incluyen,
pero no exciusivamente, Æcidoadipico, estearato de magnesio, estearato de calcio,
estearato de cinc, silicato de calcio, silicato de magnesio, aceites vegetales hidrogenados,

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cloruro de sodio, esterotex, polioxietileno, monoestearato de glicerilo, talco,
polietilenglicol, benzoato de sodio Jauril sulfato de sodio, lauril sulfato de magnesio,
estearil fumarato de sodio, aceite mineral liviano, Østeres de Æcidosgrasos como behenato
de glicerilo, (es decir COMPRITOLTM), STEAR-O-WETTM y MYVATEXTM TL. Las
5 combinaciones de estos lubricantes son factibles. En al menos una realización, el
lubricante se selecciona entre estearato de magnesio, talco y sus mezclas. El(los) lubricante(s) puede(n) estar presente(s) (cada uno) en una cantidad desde
aproximadamente 0,1% a aproximadamente 80% del peso del recubrimiento de
liberación controlada e incluye todos los valores y rangos intennedios. Por ejemplo, en
10 ciertas realizaciones ci lubricante estÆpresente en una cantidad desde aproximadamente
0,5% a aproximadamente 20%, en otras realizaciones desde aproximadamente 0,8% a aproximadamente 10% y aun en otras realizaciones en aproximadamente 1,5% del peso
del recubrimiento de liberación controlada.

15 Se pueden incluir uno o mÆs emulsionantes (tarnbiØn denominados emulsionanteso
emulgentes) en el recubrimiento de liberación controlada de las formas farmacØuticas osmóticas de ciertas realizaciones de la presente invención para facilitar la emulsificación real durante la fabricación del recubrimiento y tambiØn para aumentar o asegurar la estabilidad de la emulsion durante la vida itil del producto. Los emulsionantes ütiles para
20 la composición del recubrimiento de liberación controlada de la forma farmacØutica
osmótica incluyen, pero no exclusivamente, materiales de origen natural y sus derivados semisintØticos, como los polisacÆridos,asI como Østeres de glicerol, Øteres de celulosa,
Østeres de sorbitÆn(por ejemplo, monooleato de sorbitan o SPANTM 80) y polisorbatos
(por ejemplo, TWEENTM 80). Las combinaciones de emulsionantes son factibles.
025 El(los) agente(s) emulsionante(s) puede(n) estar presente(s) en una cantidad desde
aproximadamente 0,01% a aproximadamente 0,25% del peso del recubrimiento de
liberación controlada e incluye todos los valores y rangos intermedios. Por ejemplo, en
ciertas realizaciones el agente emulsionante estÆ presente enuna cantidad desde aproximadamente 0,01% a aproximadamente 0,15%, en otras realizaciones desde
30 aproximadamente 0,01% a aproximadamente 0,07% y aun en otras realizaciones en
aproximadamente 0,03% del peso del recubrimiento de liberación controlada.

Se pueden incluir uno o mÆsantiespumantes en el recubrimiento de liberaeión controlada
de la forma farmacØutica osmótica de ciertas realizaciones de la presente invención para
35 reducir la formación de burbuj as o de espuma durante la fabricación del recubrimiento.
Los antiespumantes ütiles para la composición del recubrimiento de liberaciOn controlada
de la forma farmacØutica osmótica incluyen, pero no exclusivamente, simeticona,

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poliglicol, aceite de silicio sus mezelas. En al menos una realización el antiespumante es Simeticona C. El antiespumante puede estar presente en una cantidad desde aproximadamente 0,01% a aproximadamente 10% del peso del recubrimiento de
liberación controlada. Por ejemplo, en ciertas realizaciones el agente antiespumante estÆ presente en una cantidad desde aproximadamente 0,05% a aproximadamente 1%, en otras realizaciones desde aproximadamente 0,1% a aproximadamente 0,3% y aun en otras realizaciones en aproximadamente 0,15% del peso del recubrimiento de liberación
controlada.

10 Se contempla que en ciertas realizaciones, se pueden usar otros excipientes compatibles
con los objetivos de la presente invención en el recubrimiento de liberaciOn controlada de
la forma farmacØutica osmOtica.

En al menos una realización, el recubrimiento de liberación controlada de la forma
15 fannacØutica osmótica incluye aproximadamente 75% de EUDRAGITfi NE301),
aproximadamente 1,5% de estearato de magnesio, aproximadamente 1,5% de talco, aproximadamente 0,03% de TWEENTM 80, aproximadamente 0,15% de Simeticona C y aproximadamente 21,82% de agua, en peso de la composición del recubrimiento de
liberaciOn controlada.
20

La forma farmacØutica osmótica de algunas realizaciones puede elaborarse segün uno
cualquiera de los mØtodos descritos aqul. En un ejemplo profØtico de ciertas
realizaciones de la forma farmacØutica osmótica de la presente invención, el proceso de
10 fabricaciOn del recubrimiento de liberaciOn controlada de la forma farmacØutica osmótica
25 puede ser hipotØticamente el siguiente: Se divide agua en dos porciones de
aproximadamente 15% y aproximadamente 85%. DespuØs se agregan el antiespumante y
el emulsionante a la porción de 15% de agua y se mezclan a 300 rpm para for-mar la
porción A. En al menos una realización, el antiespumante es Simeticona C y el
emulsionante es TWEENTM 80. DespuØs se agrega un primer lubricante a la porción de
30 85% de agua y se mezcla a 9.500 rpm para formar la porción B. En al menos una
realización, el primer lubricante es talco. DespuØs la porción A se mezcla con la porción
B, se agrega lentamente un segundo lubricante y se mezcla a 700 rpm durante toda la
noche. En al menos una realizaciOn, el segundo lubricante es estearato de magnesio. Finalmente, se agrega una dispersion acuosa de un copoilmero de un ester neutro y se
35 mezcla durante 30 minutos a aproximadamente 500 rpm. En al menos una realización, la
dispersion acuosa de un copoilmero de un ester neutro es EUDRAGITtfi NE301). La solución de recubrimiento resultante se puede usar entonces para recubrir las

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micropartIculas osnióticas subrecubiertas hasta un aumento de peso de aproximadamente 35% con los parÆmetrossiguientes: Una temperatura de entrada de aproximadamente
10°C a aproximadamente 60°C que incluye todos los valores y rangos intermedios, en algunas realizaciones entre aproximadamente 20°C y aproximadamente 40°C, y al menos
5 en una realización desde aproximadamente 25°C a aproximadamente 35’C; una
temperatura de producto entre aproximadamente 10°C y aproximadamente 60°C que
incluye todos los valores y rangos intermedios, en algunas realizaciones desde aproximadamente 15°C a aproximadamente 35°C, y en al menos una realización desde aproximadamente 22°C a aproximadamente 27°C; un flujo de aire desde
10 aproximadaniiente 10 cm/h a aproximadamente 180 cm/h que incluye todos los valores y
rangos intermedios, en algunas realizaciones desde aproximadamente 40 cm/h a aproximadamente 120 cm/h y en al menos una realización desde aproximadamente 60
cm/h a aproximadamente 80 cm/h; y una presiOn de pulverizaciOn desde
Is aproximadamente 0,5 bar a aproximadamente 4,5 bar que incluye todos los valores y
15 rangos intermedios, en algunas realizaciones desde aproximadamente 1 bar a
aproximadamente 3 bar y en al menos una realización de aproximadamente 2 bar. Las micropartIculas recubiertas resultantes se pueden descargar entonces desde la cÆmara de recubrimiento y curar en estufa con los parÆmetrossiguientes: Una temperatura de
eurado entre aproximadamente 20°C y aproximadamente 65°C que incluye todos los
20 valores y rangos intermedibs, en algunas realizaciones entre aproximadamente 30°C y
aproximadamente 55°C; y en al menos una realización a aproximadamente 40°C y un
tiempo de curado entre aproximadamente 2 horas y aproximadamente 120 horas que
incluye todos los valores.y rangos intermedios, en algunas realizaciones entre aproximadamente 10 horas y aproximadamente 40 horas, y en al menos una realización
025 de aproximadamente 24 horas. TambiØn se puede usar cualquier otra tecnologIa que dØ
como resultado la formulación del recubrimiento de liberación controlada de la forma farmacØutica osmótica que es compatible con los objetivos de la invención.

En al menos otra realización, las formas farmacØuticas osmóticas comprenden un
30 recubrimiento soluble en agua o recubrimiento de rÆpidadisolución entre la membrana
semipermeable y el recubrimiento de liberación controlada. El recubrimiento de rÆpida disolución puede 5cr soluble en la cavidad bucal y/o en ci tubo digestivo alto como estómago, duodeno, yeyuno o intestino delgado alto. Se conocen los materiales
adecuados para la fabricación del recubrimiento soluble en agua. En algunas
35 realizaciones, el recubrimiento de rÆpidadisolución puede ser soluble en la saliva, jugos
gÆstricoso fluidos Æcidos. Losmateriales que son adecuados para preparar el recubrimiento o capa soluble en agua pueden comprender, por ejemplo, gomas

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polisacÆridassolubles en agua como carragenina, fucoidan, goma ghatti, goma
tragacanto, arabinogalactano, pectina y goma xantano; sales de gomas polisacÆridas solubles en agua como alginato de sodio, tragacantina de sodio y goma gatato de sodio; hidroxialquilcelulosa soluble en agua donde el miembro alquilo es lineal o ramificado de
5 1 a 7 carbonos como, por ejemplo, hidroximetilcelulosa, hidroxietilcelulosa, e
hidroxipropilcelulosa; formadores de lÆminassintØticos a base de celulosa, solubles en
agua, como, por ejemplo, metilcelulosa y sus derivados hidroxialquilmetilcelulosa como
los iniembros elegidos entre el grupo de hidroxietilmetilcelulosa,
hidroxipropilmetilcelulosa e hidroxibutilmetilcelulosa; croscarmelosa de sodio, otros
10 polIrneros de celulosa como carboxirnetilcelulosa sódica y sus mezclas. Otros materiales
formadores de lÆrninas que se puedenusar con este propósito incluyen, por ejemplo, poli(vinilpirrolidona), alcohol polivinIlico, óxido de polietileno, una mezcla de gelatina y polivinilpirrolidona, gelatina, glucosa, sacÆridos,povidona, copovidona, copolImero de poli(vinilpirrolidona)-poli(acetato de vinilo) y sus mezclas. El recubrimiento soluble en
15 agua puede comprender otros excipientes farmacØuticos que en algunas realizaciones
pueden alterar la forma en que se comporta el recubrimiento soluble en agua. El tØcnico
con experiencia reconocerÆque los materiales indicados antes incluyen polirneros formadores de pelIcula. El recubrimiento inerte soluble en agua que cubre la pared semipermeable y bloquea el pasadizo de las formas farmacØuticas osrnOticas de la
20 presente invención, Se hace de material natural o sintØtico, el cual mediante disolución o
erosion selectiva puede permitir el desbloqueo del pasadizo permitiendo de ese modo que cornience el proceso de administración osmótica. Este recubrimiento soluble en agua
puede ser impermeable a un primer liquido externo, al mismo tiempo que es soluble en
un segundo liquido externo. Esta propiedad puede ayudar a alcanzar una liberación
25 controlada y selectiva de la sal bromhidrato de bupropion desde la forma farmacØutica
osrnótica de modo de alcanzar las velocidades de liberación in vitro deseadas,

En realizaciones en las que el nücleo de la forma farmacØutica osmótica no comprende un osmoagente, las formas farmacØuticas osrnóticas pueden coinprender un
30 subrecubrimiento osrnótico, que puede rodear el nücleo de la forma farrnacºutica
osmótica. El subrecubrimiento osmótico comprende al menos un agente osmOtico y al menos un poilmero hidrOfilo. El subrecubrimiento osmOtico de estas realizaciones
asegura la separaciOn sustancial de la sal brornhidrato de bupropion del agente osmótico
en compartimientos/capas sustancialmente separados. Esta separación puede aurnentar
35 potencialmente la estabilidad de la sal bromhidrato de bupropion reduciendo las posibles
interacciones desfavorables entre la sal bromhidrato de bupropion y el osmoagente yb
entre la sal bromhidrato de bupropion y los componentes del recubrimiento de liberaciOn

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controlada. Por ejemplo, el osmoagente puede ser de naturaleza higroseopica y puede
atraer agua que puede dar lugar a la degradacion de la sal bromhidrato de bupropion.
Puesto que el agente osmótico de estas realizaciones se puede separar sustancialmente de
la sal bromhidrato de bupropion, la sal bromhidrato de bupropion puede ser menos
5 propensa a la degradacion por el agua atraida por ci osmoagente. El recubrimiento de
liberación controlada comprende al menos un polimero de liberación controlada y opcionalmente un plastificante. Los nücleos recubiertos de la forma farmacØutica
osmOtica se pueden usar para ilenar cÆpsulas,o alternativamente se pueden coinprimir en forma de comprimidos usando excipientes adecuados. En estas realizaciones la forma
10 farmacØutica osmótica puede utilizar tanto la difusión como la osmosis para controlar la
liberación del fÆrmacoy se puede incorporar en las formas farrnacØuticas de liberación sostenida y/o de liberaciOn retardada. AdemÆs, en ciertas realizacionesel gradiente de presión osmOtica y la velocidad de liberaciOn de la sal bromhidrato de bupropion se
pueden controlar variando el nivel del agente osmOtico y/o ci nivel del polimero hidrófilo
15 en ci subrecubrimiento osmOtico, sin la necesidad de un recubrimiento sellador airededor
del subrecubrimiento osmOtico.

El polimero hidrófilo usado en un subrecubrimiento osmótico de ciertas realizaciones de
la presente invención funciona como un vehIculo para el agente osmOtico. En ciertas
20 realizaciones ci polimero hidrófilo en el subrecubrimiento osmótico no afecta de manera
importante a la liberación del fÆrmaco. En al menos una realizaciOn, el polimero
hidrófilo usado en el subrecubrimiento osmOtico no actüa como una barrera contra la
difusión para la liberación de la sal bromhidrato de bupropion. En al menos una
realización el perfil de liberación del agente osmOtico es prÆcticamenteel mismo que ci
4025 perfil de liberación de la sal bromhidrato de bupropion. Dichos poilmeros hidrOfilos
ü tiles en un subrecubrimento osmOtico de algunas realizaciones de la presente invención
incluyen a modo de ej emplo, polivinilpirrolidona, hidroxietilcelulosa,
hidroxipropilcelulosa, hidroxipropilmetilcelulosa (HPMC) de bajo peso molecular, polimetacrilato, etilcelulosa y sus mezelas. En al menos una realizaciOn, ci polimero
30 hidrófilo del subrecubrimiento osmOtico es un polimero hidrófilo de bajo peso molecular
y baja viscosidad. Se puede usar una amplia gama de poilmeros hidrófilos de bajo peso molecular y baja viscosidad en ci subrecubrimiento osmótico. Los ejemplos de
polimeros de HPMC que se pueden usar en ci subrecubrimiento osmótico incluyen PHARMACOATfi 606, PHARMACOAT fi 606G, PHARMACOAT fi 603,
35 METHOCELfi E3, METHOCELfi E5, METHOCELfi E6 y sus mezclas. El polimero
hidrOfilo del subrecubrimiento osmótico puede estar presente en una cantidad entre aproximadamente 1% y aproximadamente 30% en peso de la composición del

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subrecubrimiento osmOtico e incluye todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones ci poiImero hidrófilo estÆ presente en una cantidad entre aproximadamente 1% y aproximadamente 20%, en otras realizaciones entre aproximadamente 3% y aproximadamente 10% y aun en otras realizaciones en 7% en
peso de la composición del subrecubrimiento osrnótico.

En al menos una reaiización, el subrecubrimiento osmótico comprende aproximadamente
7% de PHARMACOATfi 606, aproximadamente 1% de cioruro de sodio y aproximadamente 92% de agua, en peso de la composición del subrecubrimiento

10 osmótico.

Un mtodo para producir ci subrecubrimiento osmótico puede ser ci siguiente. El al
menos un agente osmOtico, por ejempio cloruro de sodio, se disucive en agua. La
solución del agente osrnótico y agua se calienta luego a aproximadamente 60°C. El
15 polirnero hidrófflo se agrega luego gradualmente a la soluciOn. Se puede usar un agitador
magnØtico para ayudar a mezclar ci poilmero hidrófi.lo con la solución del agente
osmótico y agua. La solución de subrecubrimiento osmótico resuitante se puede usar a continuación para recubrir ci niicleo de la forma farmacØutica osmótica en un granulador
de lecho fluidizado, como un granulador fabricado por Glatt (Alemania) o Aerom.atic
20 (Suiza) hasta ci aurnento de peso deseado. Una temperatura de entrada entre
aproximadamente 10°C y aproximadamente 70°C que incluye todos los valores y rangos intermedios, en algunas realizaciones entre aproximadamente 30°C y aproximadamente
55°C, y en al menos una reaiización entre aproximadamente 40°C y aproximadamente
45°C; una temperatura de entrada entre aproximadamente 10°C y aproximadamente 70°C

4k5 que incluye todos los valores y rangos intermedios, en algunas realizaciones entre
aproximadamente 20°C y aproximadamente 45°C, y en al menos una reaiización entre aproximadamente 30°C y aproximadamente 35’C; una temperatura de producto entre aproximadamente 10°C y aproximadamente 70°C que incluye todos los valores y rangos intermedios, en algunas realizaciones entre aproximadamente 20°C y aproximadamente
30 45°C, y en al menos una reaiización entre aproximadamente 30°C y aproximadamente
35°C; un flujo de aire entre aproximadamente 10 cm/h y aproximadamente 180 que incluye todos los valores y rangos intermedios; en algunas realizaciones entre aproximadamente 40 cm/h y aproximadamente 120 cm/h; y en al menos una realización
entre aproximadamente 60 y aproximadamente 80 cm-/h; una presión de
35 vaporización entre aproximadamente 0,5 bar y aproximadamente 4,5 bar que incluye
todos los valores y rangos intermedios, en algunas realizaciones entre aproximadamente 1 bar y aproximadamente,3 bar, y en al menos una realización aproximadamente 2 bar; una

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temperatura de curado entre aproximadamente 10°C y aproximadamente 70°C que incluye todos los valores y rangos intermedios, en algunas realizaciones entre aproximadamente 20°C y aproximadamente 50°C, y en al menos una realización entre aproximadamente 30°C y aproximadamente 40°C; y un tiempo de curado entre aproximadamente 5 minutos y aproximadamente 720 minutos que incluye todos los
valores y rangos intermedios; en algunas realizaciones entre aproximadamente 10
minutos y aproximadamente 120 minutos, y en al menos una realización de aproximadamente 30 minutos. TambiØn se puede usar cualquier otra tecnologfa que dØ como resultado la formulación del recubrimiento del subrecubrimiento osmótico
10 compatible con los objetivos de la invención.

La relación de los componentes en el nücleo, la membrana semipermeable yio la membrana soluble en agua y/o al menos un recubrimiento de liberación controlada y/o subrecubrimiento osmótico asI como la cantidad de las diversas membranas o

15 recubrimientos aplicados se puede variar para controlar la administración de la sal
bromhidrato de bupropion ya sea predominantemente mediante difusión a travØs de la superficie de la membrana semipermeable. o predorninantemente mediante bombeo
osmótico a travØs de al menos un pasadizo en la membrana semipermeable, y
combinaciones de Østos de modo que la forma farmacØutica pueda presentar un perfil de
20 liberacjón modificada, liberación controlada, liberación sostenida, liberación extendida,
liberaciOn prolongada, liberación bifÆsica, liberación retardada o una combinaciOn de los perfiles de liberación por lo cual la velocidad de liberación in vitro de la sal bromhidrato
de bupropion es tal que despuØs de aproximadamente 2 horas se libera de
aproximadamente 0% a aproximadamente 20% en peso de la sal bromhidrato de
1925 bupropion, despuØs de aproximadamente 4 horas se libera entre aproximadamente 15% y
aproximadamente 45% en peso de la sal bromhidrato de bupropion, despuØs de aproximadamente 8 horas, se libera entre aproximadamente 40% y aproximadamente
90% en peso de la sal bromhidrato de bupropion y despuØs de aproximadamente 16
horas, se libera mÆs deaproximadamente 80% en peso de la sal bromhidrato de
30 bupropion. En las realizaciones en las que ci modo de salida de la sal bromhidrato de
bupropion comprende numerosos poros, la cantidad del agente formador de poros empleada para lograr las velocidades de disolución in vitro deseadas puede ser determinada fÆcilmente por los tØcnicos con experiencia enarea de administraciOn de fÆrmacos.
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En al menos una realización de la forma farmacØutica osmótica, ci n(icleo comprende bromhidrato de bupropion en una cantidad entre aproximadamente 40% y

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aproximadamente 99% del peso en seco del nücleo e incluye todos los valores y rangos intermedios. Por ejemplo, en algunas realizaciones ci niicleo comprende bromhidrato de bupropion en una cantidad de aproximadamente 40%, aproximadamente 45%, aproximadamente 50%, aproximadamente 55%, aproximadamente 60%,
aproximadamente 65%, aproximadamente 70%, aproximadamente 75%,
aproximadamente 80%, aproximadamente 85%, aproximadamente 90%,
aproximadamente 95% o aproximadamente 99% del peso en seco del nÆcleo.

En ciertas realizaciones, ci ni’icleo de la forma farmacØutica osmótica comprende al
10 menos un medio para aumentar la presión hidrostÆtica dentro de la membrana o ci
recubrimiento. La membrana o ci recubrimiento pueden ser una membrana
semipermeable, un recubrimiento de liberación controlada, un recubrimiento soluble en agua, un subrecubrimiento osmOtico o cualquiera de sus combinaciones. El nUcleo de la forma farmacØutica osmótica tiene una presión osmótica eficaz mayor que la del lIquido
15 circundante en ci ambiente de uso para que haya una fuerza conductora neta para que ci
agua penetre en ci nücieo. El al menos un medio para aumentar la presión hidrostÆtica dentro de la membrana o recubrimiento puede ser cualquier material que aumente la
presión osmótica del nücieo de la forma farmacØutica osmótica. El al menos un medio
para aumentar la presión hidrostÆtica dentro de la membrana o recubrimiento puede ser,
20 por ejemplo, la sal bromhidrato de bupropion, un osmoagente, cualquier material que
pueda interactuar con agua y/o un liquido biológico acuoso, hincharse y retener agua
dentro de su estructura, como por ejemplo un osmopoilmero y cualquiera de sus
cornbinaciones. El osmoagente puede set soluble o hinchable. Los ejemplos de solutos
. osmOticamente eficaces son sales y azücares inorganicos y orgÆnicos. La salbromhidrato
25 de bupropion en si misma puede ser un osmoagente o se puede combinar con uno o mÆs
de otros osmoagentes, como por ejemplo, sulfato de magnesio, cloruro de magnesio,
cloruro de sodio, cloruro de litio, sulfato de potasio, carbonato de sodio, suifito de sodio,
sulfato de litio, cloruro de potasio, carbonato de calcio, sulfato de sodio, sulfato de calcio, fosfato Æcido depotasio, lactato de calcio, d-manitol, urea, inositol, succinato de
30 magnesio, Æcido tartÆrico,Æcidossolubles en agua, alcoholes, tensioactivos y
carbohidratos como rafinosa, sacarosa, glucosa, lactosa, fructosa, algina, alginato de
sodio, alginato de potasio, carragenina, fucoridan, furcelaran, laminaran, hypnea, goma arÆbiga,goma ghatti, goma karaya, goma de algarrobo, pectina, almidón y sus mezclas.
En algunas realizaciones el nctcleo comprende ci osmoagente en una cantidad de
35 aproximadamente 15%, aproximadamente 20%, aproximadamente 25%,
aproximadamente 30%, aproximadamente 35%, aproximadamente 40%,
aproximadamente 45%, aproximadamente 50%, aproximadamente 55%,

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aproximadamente 60%, aproximadamente 65%, aproximadamente 70%, aproximadamente 75%, aproximadamente 80%, aproximadamente 85%, aproximadamente 90% o aproximadamente 95% del peso en seco del nücleo.

5 El osmoagente ütil en ciertas realizaciones de la presente invención puede ser cualquier
agente que pueda generar un gradiente de presiOn osmótica para el transporte de agua
desde el ambiente externo de uso al interior de la forma farmacØutica osmótica, Los osmoagentes tambiØn se conocen como compuestos osmóticamente eficaces, solutos osmóticos y agentes de imbibición de lIquidos osmóticos. Los osmoagentes ütiles en
10 ciertas realizaciones de la presente invención son solubles en liquidos acuosos y
biologicos, como los compuestos ionizantes, los compuestos intrInsecamente polares, los Æcidos inorgÆnicos,los Æcidos orgÆnicos, lasbases y las sales. En al menos una
realización el osmoagente es un sólido y se disuelve para formar una solución con los lIquidos embebidos en la forma farmacØutica osmótica. Se puede usar una amplia gama
15 de osmoagentes para proporcionar el gradiente de presión osmótica usado para mover la
sal bromhidrato de bupropion desde el nic!eo de la forma farmacØutica osmótica. Los ejemplos de sales inorgªnicas itiles como osmoagentes incluyen cloruro de litio, sulfato
de litio, fosfato de litio, cloruro de magnesio, sulfato de magnesio, cloruro de potasio, sulfato de potasio, fosfato de potasio, fosfato Æcido de potasio,cloruro de sodio, sulfato
20 de sodio, fosfato de sodio, sulfito de sodio, nitrato de sodio, nitrito de sodio y sus
mezclas. Los ejemplos de sales de ÆcidosorgÆnicos ütiles como osmoagentes incluyen citrato de sodio, tartrato Æcido depotasio, bitartrato de potasio, bitartrato de sodio y sus mezclas. Los ejemplos de ÆcidossOlidos ionizables iitiles como osmoagentes incluyen Æcidos tartÆrico, citrico, maleico,mÆlico,fumÆrico,tartrOnico, itacónico, adIpico,
5 succInico, mesacónico y sus mezclas. Los ejemplos de otros compuestos ütiles como
osmoagentes incluyen carbonato de potasio, carbonato de sodio, carbonato de amonio, lactato de calcio, manitol, urea, inositol, succinato de magnesio, sorbitol y carbohidratos como rafinosa, sacarosa, glucosa, lactosa, lactosa monohidratada, una mezcla de glucosa, fructosa, y mezclas de Østos. En al menos una realización el osmoagente se selecciona
30 entre cloruro de sodio, bromuro de sodio, bisulfato de sodio, tartrato Æcido depotasio,
Æcido citrico, manitol, sacarosay sus mezclas. Las combinaciones de estos osmoagentes
son permisibles. El osmoagente puede estar presente en una cantidad desde aproximadamente 0,1% a aproximadamente 50% del peso de la forma farniacØutica e
incluye todos los valores y rangos intermedios. Por ejemplo, en ciertas realizaciones el
35 osmoagente estÆpresente en una cantidad entre aproximadamente 1% y
aproximadamente 40%, y en otras realizaciones entre aproximadamente 1% y aproximadamente 20% del peso de la forma farmacØutica.

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En ciertas realizaciones, el al menos un medio para aumentar la presión hidrostÆtica
puede comprender, ademªs de un osmoagente, cualquier material que pueda interactuar
con agua y/o un liquido biologico acuoso, hincharse y retener agua dentro de su
5 estructura. En ciertas realizaciones ci al menos un medio para aumentar la presión
hidrostÆticaes un osmopoilmero, que puede ser ligeramente reticulado o no reticulado.
Los poilmeros no reticulados que se van a usar como osmopolfmeros, cuando estÆn en contacto con agua y/o liquidos biológicos acuosos, preferiblemente no se disuelven en
agua, manteniendo por consiguiente su integridad fisica. Dichos polImeros se pueden
10 elegir, por ejemplo, entre ci grupo de los derivados del ÆcidoacrIlico (çor ejemplo,
poliacrilatos, poli-metacrilato de ruetilo, poli Østeres de aiquilos superiores del (Æcido acrIlico), poli(metacrilato de etilo), poli(metacrilato de hexadecilo-co-metacrilato de
metilo), poli(acrilato de metilo-co-estireno), poli(metacrilato de n-butilo), poli(acrilato de n-butilo), poli(acrilato de ciclododecilo), poli(acrilato de bencilo), poli(acrilato de butilo),
15 poli(acrilato de secbutilo), poli(acrilato de hexilo), poli(acrilato de octilo), poli(acrilato de
decilo), poli(acrilato de dodecilo), poli(acrilato de 2-metil butilo), poli(metacrilato de adamantilo), poli(metacrilato de bencilo), poli(metacrilato de butilo), poli(metacrilato de 2-etilhexilo), poli(metacrilato de octilo), resinas acrilicas; poliacrilamidas,
poli(metacrilato de hidroxi etilo), poli(alcohol vinIlico), poli(Oxido de etileno), poli N-
20 vinil-2-pirrolidona, resinas de origen natural corno polisacÆridos (por ejemplo,dextranos,
gornas solubles en agua, almidones, almidones modificados qulmicarnente), derivados de celulosa (por ejemplo, Østeres de celulosa, Øteres de celulosa, celulosa modifleada quimicamente, celulosa microcristalina, carboxirnetilcelulosa y metilcelulosa sódicas),
. almidones, CARBOPOLTM, poilmero carboxiÆcido,CYANAMERTM, poliacrilamidas,
25 polImeros de anhIdrido indeno-maleico hinchables en agua reticulados, GOODRITETM,
Æcido poliacrIlico, Oxidode polietileno, copoilmeros injertados de almidón, AQUA-
KEEPSTM, polimero de acrilato, poliglucano diØster reticulado y cualquiera de sus

combinaciones.

30 En ciertas realizaciones, ci nc1eo de la forma farmacØutica osmótica comprende,
adernÆs, unmedio para dispensar forzadamente la sal bromhidrato de bupropion desde ci nücleo hacia el exterior de la forma farmacØutica. El al menos un medio para dispensar forzadamente la sal bromhidrato de bupropion puede 5cr cualquier material que se pueda hinchar en agua y/o liquidos biologicos acuosos y retener una fracciOn significativa de
35 agua dentro de su estructura, y que no se disuelva en agua y/o liquidos biolOgicos
acuosos, un medio para generar un gas, un soluto osrnóticamente eficaz o cualquier combinación de Østos ci cual puede estar opcionalmente rodeado por una membrana o

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recubrimiento dependiendo del medio particular usado. La membrana o recubrimiento puede ser, por ejemplo, una membrana o recubrimiento que sea esencialmente impermeable al pasaje de la sal bromhidrato de bupropion, el gas y los compuestos y que sea permeable al pasaje de agua y/o lIquidos biolOgicos acuosos. Dicho recubrimiento o
5 membrana comprende, pot ejemplo, una membrana semipermeable, una membrana
microporosa, una membrana asimØtrica, donde la membrana asimØtrica puede ser permeable, semipermeable, perforada o no perforada. En al menos una realización, el al menos un medio para dispensar forzadamente la sal bromhidrato de bupropion desde el niicleo de la forma farmacØutica osmótica comprende un medio para generar gas, donde
10 el medio para generar gas estÆrodeado, por ejemplo, por una membrana semipermeable.
En funcionamiento, cuando el medio que genera gas se embebe de agua y/o lfquidos biológicos acuosos, el medio para generar gas reacciona y genera gas, aumentando de tamafio y expandiendo asf el al menos un medio para dispensar forzadamente la sal bromhidrato de bupropion unidireccional o multidireccionalmente. El medio para
15 generar un gas comprende cualquier compuesto o compuestos, que puedan producir
efervescencia, como pot ejemplo, al menos un compuesto sólido Æcido y al menos un compuesto sólido bªsico, que en presencia de un liquido pueden reaccionar para format
un gas, como pot ejemplo, dióxido de carbono. Los ejemplos de compuestos Æcidos incluyen, ÆcidosorgÆnicOs como mÆlico, fumÆrico,tartÆrico,itacónico, maleico, cItrico,
20 adIpico, succmnico y mesacónico y ªcidos inorgÆnicos como sulfÆmico o fosfórico,
tambiØn sales Æcidas como citrato monosódico, tartrato Æcido depotasio y bitartrato de potasio. Los compuestos bÆsicos incluyen, por ejemplo,sales metÆlicas decarbonatos y bicarbonatos, como los carbonatos y bicarbonatos de metales alcalinos. Los materiales Æcidosy bÆsicosse pueden usar en cualquier proporción conveniente entre
aproximadamente 1 y aproximadamente 200 partes del al menos un compuesto Æcido a al menos un compuesto bÆsicoo entre aproximadamente 1 a aproximadamente 200 partes
del al menos un compuestobÆsicoa al menos un compuesto Æcido. Se conoce el medio
para generar gas.

30 En al menos una realización, ci al menos un medio para dispensar forzadamente la sal
bromhidrato de bupropion desde el miic!eo de la forma farmacØutica osmótica comprende cualquier material que se pueda hinchar en agua y/o lIquidos biologicos acuosos y retener una fracción importante de agua dentro de su estruetura, y que no se disuelva en agua yb lIquidos biológicos acuosos, como por ejemplo, un hidrogel. Los hidrogeles incluyen,
35 por ejemplo, polimeros hidrOfilos ligeramente reticulados, que se hinchan en alto grado
en presencia de liquidos sin disolverse, y que generalmente presentan un aumento de volumen de 5 a 50 veces. Los ejemplos no limitantes de hidrogeles incluyen

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poli(metacrilatos de hidroxialquilos), poli(acrilamida), poli(metacrilarnida), poli(N-vinil-2-pirrolidona), hidrogeles aniónicos y catiOnicos, complejos polielectroifticos, un copolfmero insoluble en agua, hinchable en agua producido formando una dispersion de copoilmeros finamente divididos de anhidrido maleico con estireno, etileno, propileno,
5 butileno o isobutileno reticulados con entre aproximadamente 0,001 y aproxirnadamente
0,5 moles de un agente reticulador poliinsaturado por mol de anhidrido maleico en un copolfmero, los polIrneros hinchables en agua o N-vinil lactamas, poli(vinil
pirrolidona)serni sOlida reticulada, hidrogeles de diØsteres de poliglucano reticulado,
hidrogeles aniónicos de monórneros N-vinil heterociclicos, geles hidrófilos ionogØnicos y
10 sus mezclas. Algunos de los osmopoilmeros e hidrogeles son intercambiables. Dicho
rnedio puede opcionalrnente estar cubierto por una membrana o recubrimiento
impermeable al pasaje de la sal bromhidrato de bupropion y los compuestos y permeable Salpasaje de agua y/o liquidos biológicos acuosos. Dicho recubrimiento o membrana
- comprende, por ejemplo, una membrana semipermeable, una membrana microporosa,
15 una membrana asimØtrica, donde la membrana asirnØtrica puede ser permeable,
semipermeable, perforada o no perforada.

En al menos otra realización, el al menos un rnedio para dispensar forzadamente la sal bromhidrato de bupropion del nücleo de la forma farmacØutica osmOtica comprende al
20 menos un soluto osmOticamente efieaz rodeado por una membrana o recubrimiento
impermeable al pasaje de la sal bromhidrato de bupropion y los compuestos y permeable
al pasaje de agua y/o lIquidos biológicos acuosos tal que el soluto osmOticamente eficaz presenta un gradiente de presión osmOtica a travØs de una membrana o recubrimiento. SDicho recubrimiento o membrana comprende, por ejemplo, una membrana
25 semipermeable, una membrana microporosa, una membrana asimØtrica, donde la
membrana asimØtrica puede ser permeable, semipermeable, perforada o no perforada.
Los solutos osmOticamente eficaces incluyen, por ejemplo, los osmoagentes descritos

antes.

30 En las realizaciones de la forma farmacØutica osmótica en las que el medio para dispensar
forzadamente la sal bromhidrato de bupropion estÆrodeado por una membrana o recubrimiento, se puede agregar al menos un plastificante a la composiciOn de la
membrana para impartir flexibilidad y elasticidad a la membrana o recubrimiento. En las realizaciones donde el rnedio para dispensar forzadamente la sal bromhidrato de
35 bupropion comprende un rnedio para generar un gas, la membrana o recubrimiento son
preferiblemente elÆsticospara evitar la ruptura de la membrana o recubrimiento durante
el periodo de administraciOn de la sal bromhidrato de bupropion. Se conocen los

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mØtodos de fabrieación de una membrana o recubrixniento. Los plastificantes, que se pueden usar en estas realizaciones incluyen, pot ejemplo, plastificantes cIclicos y
acIclicos, ftalatos, fosfatos, citratos, adipatos, tartratos, sebacatos, succinatos, glicolatos, glicerolatos, benzoatos, miristatos, sulfonamidas halogenadas fenilos,
5 poli(alquilenglicoles), poli(alquilendioles), poliØsteres de aiquilenglicoles, flalatos de
dialquilo, fiaJatos de dicicloalquilo, flalatos diarilo y flalatos de aiquilo-arilo mezclados, como por ejemplo, ftalato de dimetilo, ftalato de dipropilo, ftalato de di(2-etilhexilo),
ftalato de di-isopropilo, ftalato de diamilo y ftalato de dicaprilo; fosfatos de aiquilo y
arilo, como por ejemplo, fosfato de tributilo, fosfato de trioctilo, fosfato de tricresilo,
10 fosfato de trioctilo, fosfato de tricresilo y fosfato de trifenilo; citrato de aiquilo y Østeres
de citrato como citrato de tributilo, citrato de trietilo y acetil trietil citrato; adipatos de aiquilo, como por ejemplo, adipato de dioctilo, adipato de dietilo y adipato de di(2-metoxietilo); tartratos de dialquilo, como por ejemplo, tartratos de dietilo y tartrato de dibutilo; sebacatos de aiquilo, como por ejemplo, sebacato de dietilo, sebacato de
15 dipropilo y sebacato de dinonilo; succinatos de aiquilo, como por ejemplo, succinato de
dietilo y succinato de dibutilo; glicolatos de aiquilo, glicerolatos de aiquilo, esteres de
glicol y Østeres de glicerol, como por ejemplo, diacetato de glicerol, triacetato de glicerol, monolactato diacetato de glicerol, metil fialil etil glicolato, butil flalil butil glicolato,
diacetato de etilenglicol, dibutirato de etilenglicol, diacetato de trietilenglicol, dibutirato
20 de trietilenglicol, dipropionato de trietilenglicol y sus mezelas. Otros plastificantes
incluyen alcanfor, N-etil (o- y p-toluen) sulfonamida, bifenilo clorado, benzofenona, N-ciclohexil-p-toluensulfonamida, epóxidos sustituidos y sus mezclas.

El al menos un medio para dispensar forzadamente la sal bromhidrato de bupropion
025 desde el nücleo de ciertas realizaciones de la forma farmacØutica osmótica se pueden
ubicar de modo tal que. estØ ubicado aproximadamente en el centro dentro del nÆcleode
la forma farmacØutica osmOtica y estØ rodeado por una capa que comprenda 1a sal
bromhidrato de bupropion. Aiternativarnente, ci nücleo de la forma farmacØutica
osmótica comprende al menos dos capas en las cuales la primera capa comprende la sal
30 de bupropion, el osmoagente y/o el osmopoilmero y opcionalmente al menos un
excipiente farmacØuticamente aceptable adyacente a una segunda capa que comprende el medio para dispensar forzadamente la sal bromhidrato de bupropion. Alternativamente,
ci nic1eo de la forma farmacØutica osmótica comprende una estructura multicapa en la
cual la capa que comprende la sal bromhidrato de bupropion estÆubicada entre dos capas
35 del medio para dispensar forzadamente la sal bromhidrato de bupropion desde la forma
farmacØutica osmótica.

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Combinaciones

La presente invención tambiØn contempla las combinaciones de la sal bromhidrato de bupropion con al menos otro fÆrmaco. Por ejemplo, se proporciona una cornposicion que comprende un primer componente de bromhidrato de bupropion y un segundo
5 componente de al menos otro fªrmaco, donde cada uno de los dos componentes estÆri
presentes en una cantidad eficaz para ci tratamiento de una afección. La presente
invención proporciona, ademÆs,un mØtodo para tratar una afección, que comprende administrar a un paciente una cantidad eficaz de un primer componente de bromhidrato
de bupropion en combinación con una cantidad eficaz de al menos otro fÆrrnaco. Los
10 tØcnicos con experiencia sabrÆn o podrÆndeterminar por mØtodos conocidos quØ
combinaciones de fÆrmacos sonaceptables. Los tipos de fÆrrnacos que sepueden
seleccionar como el segundo fÆrmaco incluyena modo de ejemplo antidepresivos, ansiolIticos, antiinflamatorios esteroideos y no esteroideos, ISRS, agonistas del receptor
de serotonina, agentes antijaquecosos, analgØsicos, antiernØticos, fÆrmacos para tratar ci
15 abuso corno de la nicotina, moduladores del apetito, antivirales, vasodilatadores y
analgØsicos. Por ejemplo, ci otro fÆrmacopuede ser un antidepresivo seleccionado entre: inhibidores de la monoamino oxidasa (MAO), antidepresivos tricIclicos, inhibidores de la recaptación de serotonina, inhibidores selectivos de la recaptación de norepinefrina
(ISRN), aminocetonas, antagonistas de la serotonina, inhibidores de la recaptaciOn de
20 dopamina, inhibidores de’ la recaptación dual, potenciadores de la norepinefrmna,
potenciadores de la actividad de la serotonina, potenciadores de la actividad de la
dopa.mina y sus combinaciones. Los ejemplos de otros fÆrrnacos que se pueden combinar
con bromhidrato de bupropion incluyen citaloprarn, escitaloprarn, venlafaxina, clozapina, melperona, amperozida, iloperidona, risperidona, quetiapina, oianzapina, ziprasidona,

W25 aripiprazol, reboxetina, VIAGRAfi, sertralina, paroxetina, fluoxetina, gabapentina, Æcido

vaiproico, arnitriptilina, lofepramina, fluvoxarnina, imiprarnina, mirtazapina, nefazodona, nortripti!ina, SAM-E, buspirona y sus combinaciones. En al menos una realización, se proporciona una combinación de bromhidrato de bupropion y citaloprarn. En al menos
otra rea!izaciOn, se proporciona una combinación de bromhidrato de bupropion y
30 escitalopram. En al menos otra realización se proporciona una combinación de
bromhidrato de bupropion y venlafaxina. En al menos otra realización se proporciona
una combinación de bromhidrato de bupropion y quetiapeno.

En a!gunas realizaciones los productos de combinación pueden prepararse
35 proporcionando un sobre recubrimiento que contiene al menos otro fÆrmaco. Por
ejemplo, algunas rea!izaciones pueden comprender un nitcleo que comprende bromhidrato de bupropion, donde el nücleo estÆ en gran parte rodeado de un

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recubrimiento de liberación controlada que, a su vez, estÆrodeado en gran parte por un sobre recubrimiento que contiene al menos otro fÆrmaco. Enalgunas realizaciones el
sobre recubrimiento proporciona la liberación inmediata del otro fÆrmaco. AdemÆs del
otro fÆrmaco,ci sobre recubrimiento puede comprender al menos un poilmero hidrOfilo
5 de baja viscosidad. El polimero de baja viscosidad asegura la liberación inmediata del
otro farmaco desde ci sobre recubrimiento. En al menos una realizaciOn, ci polImero de baja viscosidad usado en el sobre recubrimiento es hidroxipropilmetilcelulosa (HPMC).
El sobre recubrimiento tambiØn puede ineluir un lubricante como talco. Por ejemplo,
estas realizaciones pueden proporcionar una liberación inmediata de al menos otro
10 fÆrmacodesde el sobre recubrimiento en una primera fase de iiberación del fÆrmaco, y
luego la subsiguiente liberación controlada del bromhidrato de bupropion desde ci nücleo recubierto con el recubrimiento de liberación controlada en una segunda fase de
liberación del fªrmaco.

S
15 AdemÆs, sepueden combinar en una forma farmacØutica combinaciones de
microparticulas de la invención, cada una con un recubrimiento funcional diferente. Por ejemplo, combinando un primer grupo de microparticulas no recubiertas, con
enmascaramiento del gusto o entØricas recubiertas con un segundo grupo de
microparticulas recubiertas de liberación sostenida o retardada, es posible lograr un perfil
20 pulsÆtil deliberación del fÆrmaco operfil cronoterapØutico. (vØase, por ejemplo, los
documentos US 5.260.068, US 6.270.805, US 6.926.909, US2002/0098232,
US2004/0 197405, US 6.635.284 o US 6.228.398).

En otras realizaciones, la combinaciOn puede comprender al menos 2 microparticulas
1025 diferentes. Por ejemplo, la combinación puede comprender un grupo de microparticulas
que aseguran la liberación controlada del bromhidrato de bupropion y un segundo grupo
de microparticulas que aseguran la liberación inmediata del otro fÆrmaco. Las
microparticulas se pueden combinar en una formulación de cÆpsulas.

30 Si bien solo se trataron combinaciones espeelficas de las diversas caracterfsticas y

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componentes de la presente invención, serÆ evidente para lostØcnicos con experiencia en
ci area, que se pueden utilizar subconjuntos deseados de las caracterIsticas y
componentes divulgados y/o combinaciones alternativas de estas caracterIsticas y componentes segün se desee.

Como se vera en los ejemplos no limitantes que se describen mÆs adelante, los recubrimientos de la invención son muy versÆtiles. Por ejemplo,la duración y ci tiempo

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del periodo de retraso se pueden controlar mediante la velocidad de hidratación y el
espesor del recubrimiento de liberación controlada. Es posible regular la velocidad de hidratación y la permeabilidad del recubrimiento de liberación controlada para que se
pueda lograr el perfil de liberación controlada deseado. No se prefiere ningin espesor en
5 particular para el recubrimiento, ya que Øste dependerÆ del perfil de liberaciOn controlada
deseado. Otros parªrnetros en cornbinación con el espesor del recubrimiento liberación controlada incluyen variar las concentraciones de uno o mÆs de los ingredientes de la composiciOn del recubrimiento de liberaciOn controlada, variar la temperatura de curado
y la duración del curado de las micropartIculas del comprimido recubierto y, en ciertas
10 realizaciones, variar el nivel de agente osmótico. El tØcnico con experiencia sabrÆ quØ
pathmetros o combinaciones de parÆrnetros cambiar para lograr un perfil deliberación controlada deseado.

ESTUDIOS DE ESTABILIDAD

15 La estabilidad mejorada de la sal bromhidrato de bupropion y las composiciones que
contienen la sal bromhidrato de bupropion, en particular cuando se las compara con la sal clorhidrato de bupropion y las composiciones que contienen la sal clorhidrato de
bupropion respectivamente, resulta evidente de los estudios de degradacion realizados
sobre el ingrediente farrnacØutico activo (IFA), solo, en presencia de excipientes y en
20 forma de comprirnidos (por ejemplo, comprimidos de liberaciOn extendida). Los
resultados Se describen con mayor detalle en los ejemplos que figuran a continuación y en
la patente de los EE.UU. rnimero 7.241.805, cuyo contenido se incorpora a la presente a modo de referencia.

25 Se llevó a cabo una cornparaciOn de la estabilidad de varias sales de bupropion, incluidas
las sales bromhidrato, clorhidrato, maleato, tosilato, fumarato, succinato, tartrato y
citrato, colocando estas sales en viales tanto abiertos como cerrados en una cmara de estabilidad mantenida a 40°C y a aproxirnadamente 75% de humedad relativa durante diversos periodos (por ejemplo, 10 dias, 13 dias, 14 dias, 20 dias, 24 dias o 32 dIas). Se
30 evaluó la estabilidad de las sales basÆndoseen la formación de los productos de
degradacion principales segün se determinó por el anÆlisis deHPLC y el % de potencia
(o ensayo) del IFA, despuØs de perlodos especfficos en la cÆmara deestabilidad.
TambiØn se estudió el efecto de la adición de disolventes, como agua, etanol y alcohol isopropIlico.
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Los resultados muestran inesperadamente que luego de diversos periodos de tiempo la sal bromhidrato de bupropion, en promedio, mostró la menor cantidad de productos de

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degradacion, en particular cuando se la compara con la sal clorhidrato. Como
consecuencia, la sal bromhidrato de bupropion mostrO una mayor estabilidad que la sal clorhidrato.

5 Se realizaron otras pruebas de estabilidad comparando directamente las sales bromhidrato
y clorhidrato de bupropion en estudios de degradación forzada. Estos estudios se
lievaron a cabo en frascos cerrados en una cÆmarade estabilidad mantenida a

aproximadamente 40°C y aproximadamente 75% de humedad relativa. A los tiempos especificados, se analizó el material de los frascos para deterniinar la presencia de
10 productos de degradación y la concentración en % (% ensayo). Se encontró
inesperadamente que la cantidad de impurezas flue generalmente inferior y la
concentración en % fue sistemÆticamente mayorpara la sal bromhidrato de bupropion en comparación con la sal clorhidrato de bupropion.

15 TambiØn se Ilevaron a cabo estudios de degradaciOn forzada sobre los IFA bromhidrato
de bupropion y clorhidrato de bupropion en presencia de los excipientes corrientes
utilizados en las formulaciones farmaeØuticas. La cantidad de los principales productos
de degradaciOn se observó a aproximadamente 24 y aproximadamente 48 horas luego del tratamiento a aproximadamente 55°C, a aproximadamente 55°C y 100% de humedad
20 relativa y a aproximadamente 105°C. Una vez mÆs, se encontró inesperadamente que la
Sal bromhidrato de bupropion mostraba la cantidad de degradación mÆs baja
(determinada por la formación de impurezas de degradacion de bupropion) en estas
condiciones.

 25 TambiØn se comparó la estabilidad de las formulaciones en comprimidos de sales de
bromhidrato y clorhidrato de bupropion. Con ambas sales, se evaiuó un comprimido
recubierto con un Unico recubrimiento de liberación controlada (por ejemplo,
ETHOCELfi o recubrimiento "EC"), asI como tambiØn un comprimido con doble
recubrimiento (con un recubrimiento de liberación controlada y un recubrimiento de
30 barrera contra la humedad). Los comprimidos se colocaron individualmente en un vidrio
de reloj sin tapar, y se expusieron a las condiciones aceleradas de aproximadamente 40°C
y aproximadamente 75% de humedad relativa en una cÆmarade estabilidad. DespuØs de
13 y 20 dIas, se determinó el contenido de las muestras y Se realizó el anÆlisis de
impurezas. Para el comprimido de clorhidrato de bupropion con un solo recubrimiento, ci
35 contenido de las impurezas de degradacion principales 3-CBZ y 852U77 fue de
aproximadamente 0,12% y 0,38% respectivamente, mientras que para los comprimidos
de bromhidrato de bupropion estos valores fueron 0,07% y 0,49%, respectivamente. Las

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demÆs impurezas dedegradación y las totales desconocidas fueron muy similares para los
dos productos; sin embargo, el valor del contenido para el producto bromhidrato fue
mayor que para el de clorhidrato. La diferencia en el contenido y en los niveles de
impurezas resultó mÆs importante en los comprimidos eon doble recubrimiento. Para el
5 mismo periodo del estudio, el contenido de clorhidrato de bupropion fue menor (95,5%
en cornparación con 98,6% para el bromhidrato) y el nivel de degradación y de impurezas desconocidas totales fue superior (3-CBZ: aproximadamente 0,28%; 852U77: aproximadamente 1,23%; 827U76: aproximadamente 0,10% y totales 1,73%) que para ci bromhidrato de bupropion (3 -CBZ: aproximadamente 0,12%; 852U77: aproximadamente
10 0,41%; 827U76: aproximadamente 0,05% y totales aproximadamente 0,75%).

Los estudios de estabilidad realizados aqul demostraron claramente la inesperada
estabilidad mejorada del bromhidrato de bupropion, en particular en comparaciOn con el clorhidrato de bupropion. Esta estabilidad mejorada se observa en la forma de IFA solo,
15 en la forma de IFA mÆs exeipientesy en los comprirnidos de liberación extendida y de
absorción mejorada. Las formulaciones farrnacºuticas que comprenden bromhidrato de bupropion mostrarÆn unamayor vida ütil y resistirÆnci almacenamiento a temperaturas y niveles de bumedad superiores en comparación con las formulaciones de clorhidrato de bupropion.
20
FORMAS POLIMORFICAS

Se sabe que las molØculas orgÆnicas puedencristalizar en formas sólidas. AdemÆs,ci
mismo compuesto orgÆnico puede tenerdiferentes disposiciones cristalinas en la forma sOlida, dependiendo de las condiciones en que se formó ci producto cristalino. Este
25 fenómeno se conoce comünmente como polirnorfism.o. Se emprendió un estudio para
explorar las formas polimórficas del bromhidrato de bupropion. Las formas cristalinas de
los productos obtenidos en este estudio se determinaron por difracción de rayos X de
polvos (PXRD). Se usó un instrurnento RIGAKU miniflex (generador de radiación de
Cu K de 30 KY, filtro de Ni) para obtener los datos de PXRD. Los resultados Se
30 describen por ejemplo en la patente de los EE.UU. N° 7.241-805, cuyo contenido se
ineorpora a la presente a modo de referencia.

CRISIS CONVULSIVAS INDUCIDAS POR BUPROPION
Los estudios de EEG, mediante ci uso de electrodos implantados para detectar la
35 actividad eiectroencefaiografica on ratas concientes, analizaron los efeetos de dosis
equimolares de clorhidrato de bupropion y bromhidrato de bupropion sobre la actividad
del sistema nervioso central luego de la adrninistración intraperitoneal. Los resuitados

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(descritos con mayor detalle mÆsadelante) demuestran que el bromhidrato de bupropion tiene una menor potencia para inducir convulsiones asI como tanibiØn para reducir la gravedad de las crisis convulsivas en comparación con el clorhidrato de bupropion. En contraste con el clorhidrato de bupropion, la sal bromhidrato de bupropion indujo menos convulsiones en menos animales. En otras comparaciones, se observó sorprendentemente
que la gravedad de las crisis observadas con el bromhidrato de bupropion era significativamente menor que la gravedad de las crisis convulsivas en los animales a los
que se les administró clorhidrato de bupropion.

10 La maxima dosis del bromhidrato de bupropion administrada en los estudios en ratas fue de 100 mg/kg, y en los estudios en ratones fue de 150 mg/kg. La dosis de 150 mg/kg equipara aproximadamente a 37,5 mg/kg de bromuro o aproximadamente 48,3 mg/kg de bromuro de sodio. Estos niveles terapØuticos de bromuro en los cuales la incidencia y/o la gravedad de las crisis convulsivas inducidas por bupropion son
15 reducidas, son sorprendentemente mÆs bajos que los que seesperarlan de los datos
farmacologicos conocidos que estudian las dosificaciones mfnimas de bromuro
necesarias para cualquier beneficio terapØutico observable. Como Se mencionó
anteriormente, el nivel de bromuro necesario para tratar las crisis convulsivas inducidas
por pentilenotetrazol es de 910 mg/kg [M.S. Grewal et al., Journal of Pharmacology And
20 Experimental Therapeutics, Vol. 112, Issue 1, 109-115, 1954].

30

Ciertas realizaciones de la presente invención se refieren a composiciones de bupropion que comprenden cantidades farmacØuticamente seguras y eficaces de
bromhidrato de bupropion; en donde dichas composiciones inesperadamente producen menos incidencias de crisis convulsivas y/o crisis convulsivas menos graves asociadas a
la administración de bromhidrato de bupropion que una composición por Jo demÆs
similar o idØntica que contenga una cantidad molar equivalente de clorhidrato de
bupropion.

Realizaciones adicionales

Otras realizaciones de la invenciOn descritas aqul y habilitadas por la presente
descripción incluyen las siguientes:

35 Algunas realizaciones incluyen bromhidrato de bupropion y 3tcloro2bromo
propiofenona. La 3’-cloro-2-bromo-propiofenona es una impureza asociada a la
preparación de bromhidrato de bupropion. En algunas realizaciones, la 3-cloro-2-bromo-

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propiofenona estÆpresente en una cantidad que no es genotóxica, o en una cantidad que resultarfa en una exposiciOn diana no mayor a ("NMA") aproximadamente 1,5 jg/dia en
ci producto del fÆrmaco. Algunas realizacionescontienen menos de aproximadamente 1,5 jig de 3’-cloro-2-bromo-propiofenona. Por ejemplo, en aigunas realizaciones la impureza
5 de 3’-cloro-2-bromo-propiofenona estÆpresente en una cantidad menor a
aproximadamente 1,5tg, 1,4g, 1,3 jig, 1,2ig, 1,1[g, 1,0j.ig, 0,9jig, 0,8jig, 0,7tg, 0,6jig,
0,5 jig, 0,4jig, 0,3 jig, 0,2 jig, 0,1 jig, 0,09jig, 0,08 jig, 0,07jig, 0,06jig, 0,05 jig, 0,04jig,
0,03 jig, 0,02jig, o 0,01 jig, incluidos todos los valores y subrangos intermedios. En al
menos una realización la impureza de 3tcloro2bromopropiofenona estÆpresente en
10 cantidades indetectabies en donde el lImite de detección es 1,Ojig o lppm.

En algunas realizaciones el producto de degradacion del Æcido3-ciorobenzoico estÆ limitado en ci producto del fÆrmaco a aproximadamente0,7% o menor. En al menos una reaiizaciOn el producto de degradacion del ªcido 3-ciorobenzoico estÆlimitado en la
15 composición a aproximadamente 0,5% o menor. En al menos otra realización el
producto de degradación del ªcido 3-clorobenzoico estÆ limitado enla composiciOn a aproximadamente 0,3% o menor.

En algunas realizaciones ci contenido de humedad en el producto del thrinaco estª
20 limitado a no mÆsde aproximadamente 2,0%. En algunas realizaciones el contenido de
humedad estÆlimitado a no mÆs de aproximadamente2,0% luego de un tiempo de almacenamiento de aproximadamente 1 minuto cuando se almacenan en un recipiente
cerrado utilizando un aparato de Karl Fischer y ci MØtodo USP 1. Por ejemplo, en
. aigunas realizaciones el contenido de humedad luego de un tiempo de almacenamiento
25 de aproximadamente 1 minuto cuando se almacenan en un recipiente cerrado utilizando
un aparato de Karl Fischer y ci MØtodo USP 1, es menor que aproximadamente 2,0%,
1,9%, 1,8%, 1,7%, 1,6%, 1,5% 1,4%, 1,3%, 1,2%, 1,1%, 1,0%, 0,9%, 0,8%, 0,7%, 0,6%,
0,5%, 0,4%, 0,3%, 0,2% o 0,1%, incluidos todos los valores y subrangos intermedios.

30 En otra realización existe un comprimido que comprende (i) un nücleo y (ii) un
recubrimiento de liberación controlada, comprendiendo dicho nücleo:
(a) bromhidrato de bupropion;
(b) aglutinante (por ejemplo, alcohol polivinflico) y
(c) lubricante (por ejemplo, beheriato de glicerilo - Compritolfi 888);
35 comprendiendo dicho recubrimiento de liberación controlada (por ejemplo,
"SMARTCOAT"):

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(d) poiImero formador de peilcula insoluble en agua y permeable al agua (por ejemplo, etilcelulosa grado PR 100);
(e) plastificante (por ejemplo, polietilenglicol 4000, sebacato de dibutilo o una mezcla de Østos);
5 (1) polImero soluble en agua (por ejemplo, polivinilpirrolidona - Povidonafi USP);
en donde en ci recubrimiento de liberaciOn controlada la relación de (d):(e):(f) desde aproximadamente 3:1:4 a aproximadamente 5:1:2; o desde aproximadamente 7:2:6 a aproximadamente 19:5:18; o aproximadamente 13:4:12; o aproximadamente 13:6:16; comprendiendo el comprimido opcionalmente, ademÆs, unrecubrimiento de barrera
10 contra la humedad;
comprendiendo dicho recubrimiento de barrera contra la humedad opcional:
(g) un poilmero entØrico (por ejemplo, un polImero acrilico como copoilmero de Æcido metacrIlico tipo C - Eudragitfi L30 D-55);
(h) un potenciador de la penetración (por ejemplo, diOxido de siiicio - Syloidfi 244FP)
15 (i) plastificante (opcional) - (por ejemplo, mezcla de citrato de trietilo y polietilenglicol
4000 - Carbowaxfi 4000).

En otra realización existe una composición farrnacØutica que se administra una vez al dIa con liberación modificada que comprende 522 mg de bromhidrato de bupropion,
20 proporcionando dicha composiciOn un perfil plasmÆticoin vivo seleccionado de:
TmÆxmedio desde aproximadamente 2 horas a aproximadamente 7 horas;
CmÆx media desdeaproximadamente 113 ng/ml a aproximadamente 239 ng/ml;
CmIn media desde aproximadamente 18 nglml a aproximadamente 44 ng/ml y
AUCO-t media desde aproximadamente 1236 ng-hr!ml a aproximadamente 2224 ng-
hr/mi.

En otra realización existe una composición farmacØutica que se administra una vez al dIa con liberaciOn modificada que comprende 348 mg de bromhidrato de bupropion, proporcionando dicha composicion un perfil piasmÆticoin vivo seleccionado de:
30 TmÆx medio desde aproximadamente2 horas a aproximadamente 7 horas;
CmÆx media desdeaproximadamente 96 ng/ml a aproximadamente 172 ng/ml;
Cmin media desde aproximadamente 17 ng/ml a aproximadamente 36 ng/ml y
AUCO-t media desde aproximadamente 1063 ng-hr/mi a aproximadamente 1755 ng-
hr/mi.

En otra realización existe una cornposición farmacØutica que se administra una vez al dia
con liberación modificada que comprende bromhidrato de bupropion, proporcionando

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dicha cornposiciOn un TmÆxmedio desde aproximadamente 2 horas a aproximadamente
7 horas.

En otra realización existe una composiciOn farmacØutica que se administra una vez a! dia
5 eon liberación modificada que comprende bromhidrato de bupropion, proporcionando
dicha composición un TniÆx medioque es sustancialmente equivalente al de una
composición farmacØutiea que se administra una vez al dia con liberaciOn modificada que comprende clorhidrato de bupropion.

10 En otra realizaeión existe una composieión farmacØutiea que se administra una vez al dia
con liberaciOn modificada que comprende brornhidrato de bupropion, proporcionando
dicha eomposición un TmÆxmedio que estÆentre aproximadamente 80% y
aproximadamente 125% de!a composicion farmacØutica que se administra una vez a! dia Sconliberación modificada que comprende clorhidrato de bupropion.

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En otra realización existe una cornposiciOn farmaeØutiea que se administra una vez al dia
eon liberación modificada que comprende bromhidrato de bupropion, proporcionando
dicha composición una Cmªx media que es sustancialmente equivalente a la de una
composición farrnacØutica que se administra una vez al dia con liberación modificada que
20 comprende clorhidrato de bupropion.

En otra rea!ización existe una composicion farmacØutica que se administra una vez al dia
con liberación modificada que comprende bromhidrato de bupropion, proporcionando
. dicha composiciOn una CmÆx media queestÆ entreaproximadamente 80% y
25 aproximadamente 125% de la composición farmacØutica que se administra una vez al dia
con liberación modificada que comprende clorhidrato de bupropion.

En otra realizaciOn existe una composiciOn farmacØutica que se administra una vez al dIa
con liberación modificada que comprende brornhidrato de bupropion, proporcionando
30 dicha composición una CmIn media que es sustancialmente equivalente a la de una
composiciOn farmacØutica que se administra una vez al dia con liberación modificada que comprende clorhidrato de bupropion.

En otra realización existe una composición farmacØutica que se administra una vez a! dia
35 eon liberaciOn modificada que comprende brornhidrato de bupropion, proporcionando
dicha composiciOn una CmIn media que estÆ entreaproximadamente 80% y

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aproximadamente 125% de la composición farmacØutica que se administra una vez al dia con liberación modificada que comprende clorhidrato de bupropion.

En otra realización existe una composición farmacØutica que Se administra una vez al dia
5 con liberación modificada que comprende bromhidrato de bupropion, proporcionando
dicha composición una AUCO-t media que es sustancialmente equivalente a la de una composicion farmacØutica que se administra una vez al dia con liberación modificada que comprende clorhidrato de bupropion.

10 En otra realizaciOn existe una composiciOn farmacdutica que se administra una vez al dia
con liberación modificada que comprende bromhidrato de bupropion, proporcionando
dicha composición una AUCO-t media que estÆ entre aproximadamente80% y aproximadamente 125% de la eomposición farmacdutica que se administra una vez at dia con!iberaciOn modificada que comprende clorhidrato de bupropion.
15

En otra realización existe una composiciOn fannacØutica de liberación modificada que comprende:
un nücleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de
bupropion y
20 un recubrimiento polimdrico de liberación controlada que comprende un polimero
insoluble en agua y un polimero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
en donde dicha cantidad de bromhidrato de bupropion liberada en un tiempo entre aproximadamente 0 horas a aproximadamente 16 horas en presencia de al menos 5% de
1025 etanol, utilizando un Aparato I USP a 75 rpm y 37 1 0,5°C, es menor que la cantidad de
bromhidrato de bupropion liberado en el mismo tiempo en HC1 0,1 N utilizando un
Aparato I USP a 75 rpm y 37 – 0,5°C.

En otra realización existe una composición farmacØutica de liberación modificada que
30 comprende:
un nilcleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de
bupropion y
un recubrimiento polimØrico de liberaciOn controlada que comprende un polimero
insoluble en agua y un polimero soluble en agua;
35 en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
en donde dicha cantidad de bromhidrato de bupropion liberada en un tiempo entre aproximadamente 0 horas a aproximadamente 16 horas en presencia de at menos 5% de

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etanol, utilizando un Aparato I USP a 75 rpm y 37 – 0,5°C, es menor que
aproximadamente el 125% de la cantidad de bromhidrato de bupropion liberado en el
mismo tiempo en HCI 0,1 N utilizando un Aparato I USP a 75 rpm y 37 – 0,5°C.

5 En otra realizaciOn existe una composición farrnacØutica de liberación modificada que
comprende:
un nücleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de bupropion y
un recubrimiento polimØrico de liberación controlada que comprende un polImero
10 insoluble en agua y un poilmero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
en donde no tiene lugar la absorciOn rÆpidade la dosis en presencia de HC1 0,1 N con

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EtOH al 40%.

15 En otra realización existe un mØtodo para reducir la absorción rÆpida de la dosis que
consiste en administrar a un sujeto una cornposición farmacØutica de liberación
modificada que comprende:
un nücleo que comprende una cantidad terapØuticamente eficaz de brornhidrato de bupropion y
20 un recubrimiento polimØrico de liberaciOn controlada que comprende un poilmero
insoluble en agua y un pollinero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento.

En otra realización existe una composiciOn farmacØutica que comprende 522 mg de
25 bromhidrato de bupropion, proporcionando dicha cornposición un perfil plasmÆtico in
vivo seleccionado de:
TmÆx mediodesde aproximadamente 2 horas a aproximadamente 7 horas;
CmÆx mediadesde aproximadamente 115 ng/ml a aproximadamente 235 ng/ml;
Crnfn media desde aproximadamente 20 ng/ml a aproximadamente 40 ng/ml y
30 AUCO-24 hr desde aproximadamente 1240 ng-hr/rnl a aproximadamente 2220 ng-hr/ml.

En otra reaiización existe una composición farmacØutica que comprende 522 mg de bromhidrato de bupropion, proporcionarido dicha composición un peruil plasmÆtico in
vivo seleccionado de:
35 Trnªx medio de aproximadamente 4 horas;
CmÆxmedia menor que aproximadamente 200 ng/ml y
AUCO-24hr media mayor que aproximadamente 2000 ng-hr/rnl.

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En otra realización existe una composición farmacØutica que se administra una vez al dIa con liberación modificada que comprende bromhidrato de bupropion, proporcionando
dicha composición un TmÆx medioque es sustancialmente equivalente al de una
5 composición farmacØutica que se administra una vez al dIa con liberaciOn modificada que
comprende clorhidrato de bupropion en lugar de bromhidrato de bupropion.

En otra realización existe una composición farmacØutica que se administra una vez al dIa
con liberación modificada que comprende bromhidrato de bupropion, proporcionando
10 dicha composición un TinÆx rnedioque estÆentre aproximadamente 80% y
aproximadamente 125% de la composiciOn farmacØutica que se administra una vez al dIa con liberación modificada.que comprende clorhidrato de bupropion en lugar de
bromhidrato de bupropion.

15 En otra realización existe un comprimido de liberación modificada que comprende:
(i) un nücleo que comprende
(a) una cantidad terapØuticamente eficaz de bromhidrato de bupropion,
(b) un aglutinante y
(c) un lubricante y
20 (ii) un recubrimiento polimerico de control de la liberación que rodea al menos
parcialmente dicho recubrimiento;
en donde dicho comprimido de liberación modificada asegura la liberación controlada de
dicho bromhidrato de bupropion de dicho comprimido de liberación modificada en un
perfodo de aproximadamente 24 horas y
025 en donde dicho comprimido de liberación modificada tiene una estabilidad mejorada en
comparación con un comprimido de liberación modificada por lo demÆs similar o
idØntico que comprende una cantidad molar equivalente de clorhidrato de bupropion en
lugar de bromhidrato de bupropion cuando cada uno de ellos se almacena durante a!
menos 12 meses a aproximadamente 25°C y a aproximadamente 60% de humedad
30 relativa.

En otra realización existe un comprimido de bromhidrato de bupropion de liberación modificada adecuado para la administración oral que comprende
(i) un nücleo que comprende
35 (a) una cantidad terapØuticamente eficaz de bromhidrato de bupropion,
(b) un aglutinante y
(c) un lubricante y
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(ii) un recubrimiento polimØrico de liberaciOn controlada que rodea al menos
parcialmente dicho recubrimiento y;
(iii) un producto de degradación seleccionado de Æcido3-clorobenzoico, 827U76, 20U78, 852U77 y mezclas de Østos;
5 en donde dicho comprimido de bromhidrato de bupropion de liberaciOn controlada
contiene menor cantidad de dicho producto de degradación en comparación con un comprimido de liberación modificada por lo demÆs similaro idØntico que contiene una cantidad molar equivalente de clorhidrato de bupropion en lugar de bromhidrato de bupropion,
10 cuando ci comprimido de bromhidrato de bupropion de liberación controlada y el
comprimido de liberación modificada por Jo dernÆssimilar o idØntico que contiene clorhidrato de bupropion se almacenan cada uno durante al menos 12 meses a 25°C y S60%de humedad relativa luego de la formuiación del comprimido.

15 En otra realización existe un comprimido de liberación modificada que comprende:
una cantidad terapØuticamente eficaz de bromhidrato de bupropion,
en donde aproximadamente 12 meses despuØs de la forrnulación de dicho comprimido de liberación modificada a aproximadamente 37– 0,5°C, se libera desde aproximadamente
0% a 40% de dicho bromhidrato de bupropion luego de 2 horas; se libera desde
20 aproximadamente 40% a aproximadamente 75% de dicho bromhidrato de bupropion
luego de 4 horas; se libera no menos de aproximadamente 75% de dicho bromhidrato de bupropion luego de 8 horas y se libera no menos de aproximadamente 85% de dicho bromhidrato de bupropion luego de 16 horas en 900 ml de HC1 0,1 N utilizando un

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aparato USP Tipo 1 con una velocidad de rotación de 75 rpm.
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En otra realización existe una cornposición farmacØutica de liberaciOn modificada que comprende:
(i) un nücieo que comprende una cantidad terapØuticamente eficaz de bromhidrato de bupropion y
30 (ii) un recubrimiento polimØrico de liberaciOn controlada que comprende un pollmero
insoluble en agua y un polfrnero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
en donde dicha composicion es resistente a la absorción rÆpida de la dosis inducida por
alcohol.
35

En otra realización existe una composicion farmacØutica de liberación modificada que comprende:

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(i) un nücleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de bupropion y
(ii) un recubrimiento polimØrico de liberaciOn controlada que comprende un polimero insoluble en agua y un polimero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
en donde la velocidad de liberación del bromhidrato de bupropion en tin medio de disolución que contiene alcohol es mÆs lenta que lavelocidad de liberación del bromhidrato de bupropion en tin medio de disolución que no contiene alcohol.

10 En otra realización existe una composición farmacØutica de liberación modificada que
comprende:
(i) un nücleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de bupropion y
(ii) un recubrimiento polimØrico de liberación controlada que comprende un polimero
15 insoluble en agua y un polimero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
donde la cantidad de bromhidrato de bupropion liberada en un tiempo de
aproximadamente 0 horas a aproximadamente 16 horas en un medio de disolución que
contiene aproximadamente 40% de EtOH y 60% de HC1 0, IN, utilizando un Aparato
20 USP Tipo 1 a 75 rpm, no es mayor que la cantidad de bromhidrato de bupropion liberada
en el mismo tiempo en un medio de disolución que contiene aproximadamente 100% de
HC1 0,1N utilizando tin Aparato USP Tipo 1 a 75 rpm.

En otra realización existe una composición farrnacØutiea de liberación modificada que
025 comprende:
(i) un nücleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de
bupropion y
(ii) un recubrimiento polimØrico de liberación controlada que comprende un polimero insoluble en agua y un polimero soluble en agua;
30 en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento y
donde la cantidad de bromhidrato de bupropion liberada en un tiempo de
aproximadamente 0 minutos a aproximadamente 120 minutos en tin medio de disolución
que contiene aproximadamente 40% de EtOH y 60% de HC1 0,1N, utilizando un Aparato USP Tipo 1 a 75 rpm, no es mayor que la cantidad de bromhidrato de bupropion liberada
35 en el mismo tiempo en tin medio de disolución que contiene aproximadamente 100% de
HC1 0,IN utilizando tin Aparato USP Tipo 1 a 75 rpm.

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En otra realizaciOn existe un mØtodo para resistir la absorción rÆpida de la dosis de bromhidrato de bupropion inducida por alcohol que consiste en administrar a un sujeto
una cornposición farrnacØutica de liberación modificada, comprendiendo dicha composición:
5 (i) un nücleo que comprende una cantidad terapØuticarnente eficaz de bromhidrato de
bupropion y
(ii) un recubrimiento polimØrico de liberaciOn controlada que comprende un polimero insoluble en agua y un polimero soluble en agua;
en donde dicho recubrimiento rodea al menos una parte de dicho recubrimiento.
10

En otra realización existe un mØtodo para tratar un sujeto en riesgo de absorción rÆpida
de la dosis de bromhidrato de bupropion inducida por alcohol y que necesita tratamiento con bupropion, en la que dicho mØtodo comprende administrar a un sujeto una
composición farmacØutica de liberación modificada, comprendiendo dicha composición:
15 (i) un nücleo que comprende una cantidad terapØuticamente eficaz de bromhidrato de
bupropion y
(ii) un recubrimiento polimØrico de liberación controlada que comprende un polimero
insoluble en agua y un polimero soluble en agua;
en donde dicho recubrimiento rodea al menos una partede dicho recubrimiento.
20

En otra realización existe una cornposición que comprende bromhidrato de bupropion y
3 ’-cloro-2-bromo-propiofenona.

. En otra realIzación existe una composición que comprende bromhidrato de bupropion y
25 menos de aproximadamente 1,5 tg de 3’-cloro-2-brorno-propiofenona.

En otra realización existe una composición que comprende bromhidrato de bupropion y
menos de aproximadamente 1,0 jig de 3’-cloro-2-bromo-propiofenona.

30 En otra realización existe una composición de liberación modificada que contiene
bromhidrato de bupropion en donde el contenido de humedad no es mayor que aproximadamente 2,0% en dicha composiciOn luego de un tiempo de almacenamiento de aproximadamente 1 minuto cuando se la almacena en un recipiente cerrado utilizando un aparato de Karl Fischer, MØtodo USP 1.
35

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En otra realización existe una composición que contiene bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable, en donde la cantidad de bromhidrato
de bupropion se selecciona de 174 mg, 348 mg y 522 mg.

En otra reaiización existe un comprimido de liberación modificada que contiene
bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable, en donde la cantidad de bromhidrato de bupropion se selecciona de 174 mg, 348 mg y 522
Mg.

10 En otra realización existe un comprimido de iiberación modificada que contiene
bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable, en donde la cantidad de bromhidrato de bupropion se selecciona de 174 mg, 348 mg y 522
Mg; y en ci que el bromhidrato de bupropion estÆcontenido en el interior de un nücleo
del comprimido que comprende ademÆsun recubrimiento de liberaciOn controlada que
15 recubre el nücleo.

En otra reaiización existe una composición que contiene al menos bromhidrato de bupropion en la concentración especificada en uno de A, B y C de la siguiente Tabla mezelado con uno o mÆscomponentes adicionales de las columnas A, B y C de la
20 siguiente Tabla:
B C
Componente
Bromhidrato de bupropion 174 mg 348 mg 522 mg
Alcohol polivinIiico 5,8 mg 11,6 mg 22,5 mg
Behenato de giicerilo 5,8 mg 11,6 mg 22,5 mg
Peso del recubrimiento del

comprimido de referencia
(mg)

185,6 mg 371,2 mg 567 mg

Etiicelulosa 100, NF 15,4 mg 16,4 mg 18,13 mg
Povidona (K-90) 9,5 mg 10,2 mg 21,87 mg
Polietiiengiicoi 4000 3,4 mg 3,7 mg 5,33 mg
Sebacato de dibutilo (DBS) 1,7 mg 1,8 mg 2,67 mg
umento de peso del
recubrimiento de referencia
(mg)

30 mg F 32 mg 1- 48 mg

Cera de Carnauba Trazas Trazas S/A

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Alcohol etIlico Eliminado por Eliminado por Eliminado por
desnaturalizado, graduacion evaporación evaporación evaporación
200

Alcohol etIlico, graduación Eliminado por Eliminado por Eliminado por
190 evaporaciOn evaporación evaporaciOn
igua purificada Eliminado por Eliminado por Eliminado por
evaporación cvaporación evaporación
[inta negra Opacode R Trazas Trazas Trazas
Alcohol isopropflico, 99% Ninguno Ninguno Ninguno
Peso final del comprimido 216 mg 403 mg 615 mg
impreso (mg)

En otra realización existe una composición que contiene al menos aproximadamente 522 mg de bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable. En otros aspectos de esta realización la composición estÆ en forma de comprimido. En
otros aspectos de esta realización la cornposición estÆ en formade formulación de
!iberación modificada. En otros aspectos de esta realización la composición estÆ en
forma de comprimido y el bromhidrato de bupropion estÆ contenidoen el interior de un micleo del comprimido que comprende ademÆsun recubrimiento sobre el nücleo. En
otros aspectos de esta realización el recubrimiento es un recubrimiento de liberaciOn
10 controlada.

En otra realización existe una composición que comprende bromhidrato de bupropion y

10 al menos un excipiente farmacØuticarnente aceptable;
en donde la administración de una cantidad de bromhidrato de bupropion a una prirnera
15 rata resulta en una menor incidencia de crisis convulsivas y/o crisis convulsivas menos
graves inducidas por bupropion cuando se la compara con la incidencia y/o gravedad de
las crisis convulsivas inducidas por bupropion corno resultado de la administración de
una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata y,
en donde la incidencia y/o la gravedad de las crisis convulsivas inducidas por bupropion
20 son medidas por medio de un electroencefalograrna utilizando tin electrodo profundo
implantado en el hipocampo.

En otra realización existe un comprimido de liberación modificada que comprende bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable;
25 en donde la administración de una cantidad de bromhidrato de bupropion a una primera
rata resulta en una menor incidencia de crisis convulsivas y/o crisis convulsivas menos

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graves inducidas por bupropion cuando se la compara con la incidencia y/o gravedad de las crisis convulsivas inducidas por bupropion como resultado de la administración de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata y,
en donde la incidencia y/o la gravedad de las crisis convulsivas inducidas por bupropion
son medidas por medio de un electroencefalograma utilizando un electrodo proftindo implantado en el hipocampo.

En otra realización existe una composición que comprende brothhidrato de bupropion y
al menos un excipiente farmacØuticamente aceptable;
10 en donde la administración de aproximadamente 100 mg/kg de bromhidrato de bupropion
a una primera rata resulta en una menor incidencia de crisis convulsivas y/o crisis convulsivas menos graves inducidas por bupropion cuando se la compara con la
incidencia y/o gravedad de las crisis convulsivas inducidas por bupropion coma resultado
de la administración de una cantidad molar equivalente de clorhidrato de bupropion a una
15 segunda rata y,
en donde la incidencia ybo la gravedad de las crisis convulsivas inducidas por bupropion
son medidas por medio de un electroencefalograma utilizando tin electrodo profundo implantado en el hipocampo.

20 En otra realización existe un mØtodo para tratar a un sujeto en riesgo de sufrir crisis
convulsivas inducidas por bupropion que necesita tratamiento con bupropion,
comprendiendo dicho mØtodo:
administrar una composiciOn que contiene bromhidrato de bupropion a dicho sujeto en
una cantidad suficiente para tratar dicho sujeto.
 5

En otra realización existe un mØtodo para tratar a un sujeto en riesgo de sufrir crisis convulsivas inducidas por bupropion que necesita tratamiento con bupropion, comprendiendo dicho mØtodo:
administrar una composición que contiene bromhidrato de bupropion a dicho sujeto en
30 una cantidad suficiente para tratar dicho sujeto en donde la composición contiene una
cantidad de bromhidrato d.e bupropion seleccionada de 174 mg, 348 mg y 522 mg.

En otra realización existe un mØtodo para tratar a un sujeto en riesgo de sufrir crisis convulsivas inducidas par bupropion que necesita tratamiento con bupropion,
35 comprendiendo dicho mØtodo:
administrar una composición que contiene bromhidrato de bupropion a dicho sujeto en una cantidad suficiente para tratar dicho sujeto, en donde la composición contiene una

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cantidad de brornhidrato de bupropion seleccionada de 174 mg, 348 mg y 522 mg en donde la composición estÆ en forma de comprimido de liberaciOn modificada, en donde el comprirnido contiene un recubrimiento de liberación controlada y en donde la administración comprende la administración oral.

En otra realización existe un mØtodo para reducir la incidencia de las crisis convulsivas inducidas por bupropion que comprende: administrar una cantidad farmacØuticarnente
eficaz de bromhidrato de bupropion a un sujeto que necesita la administración de
bupropion;
10 en donde la incidencia y/o gravedad de las crisis convulsivas inducidas por bupropion
como resultado de la adrninistración de bromhidrato de bupropion es menor que la
incidencia y/o gravedad de las crisis convulsivas inducidas por bupropion como resultado
de la administración de una cantidad molar equivalente de clorhidrato de bupropion.

15 En otra realización existe un mØtodo para reducir la incidencia y/o gravedad de las crisis
convulsivas inducidas por bupropion que comprende:
administrar una cantidad farmacØuticamente eficaz de bromhidrato de bupropion a un
sujeto que necesita la administraciOn de bupropion;
en donde la administración de aproximadamente 100 mg/kg de bromhidrato de bupropion
20 a una primera rata resulta en una menor incidencia de crisis convulsivas y/o crisis
convulsivas menos graves inducidas por bupropion cuando se la compara con la
incidencia y/o gravedad de las crisis convulsivas inducidas por bupropion como resultado
de la adrninistraciOn de una cantidad molar equivalente de clorhidrato de bupropion a una

1025

segunda rata y,
en donde la incidencia y/o la gravedad de las crisis convulsivas inducidas por bupropion
en la primera y segunda rata son medidas por medio de un electroencefalograma
utilizando un electrodo profundo implantado en el hipocampo.

En otras realizaciones de evaluación de la incidencia y/o gravedad de las crisis
30 convulsivas inducidas por bupropion, se realiza una evaluación fenotIpica del sujeto. Por
ejemplo, una crisis convulsiva suave se caracteriza por un pequeflo sacudimiento de la cabeza, una crisis convulsiva moderada se caracteriza por algunos sacudimientos de la cabeza y las crisis convulsivas graves se caracterizan por un fuerte sacudimiento de la

cabeza.
35

En otra realización existe un mdtodo para reducir la incidencia y/o gravedad de las crisis convulsivas inducidas por bupropion mediante la administración conjunta de una sal de

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bromuro con una sal de bupropion, en donde la sal de bromuro se administra en una cantidad menor que aproximadamente 3,5 mg/kg. En otros aspectos de esta realización, la sal de bromuro se administra en cantidades entre aproximadamente 1,0 y
aproximadamente 3,5 mg/kg, e incluyen 1,1 mg/kg, 1,2 mg/kg, 1,3 mg/kg, 1,4 mg/kg, 1,5
5 mg/kg, 1,6 mg/kg, 1,7 mg/kg, 1,75 mg/kg, 1,8 mg/kg, 1,9 mg/kg, 2,0 mg/kg, 2,1 mg/kg,
2,2 mg/kg, 2,3 mg/kg, 2,4 mg/kg, 2,5 mg/kg, 2,6 mg/kg, 2,67 mg/kg, 2,7 mg/kg, 2,8
mg/kg, 2,9 mg/kg, 3,0 mg/kg, 3,1 mg/kg, 3,2 mg/kg, 3,3 mg/kg, 3,4 mg/kg y todos los valores y rangos intermedios. En otros aspectos de esta realización, la sal de bromuro es
una sal de bromuro de sodio. En otros aspectos de esta realizaciOn, la sal bupropion es
10 una sal clorhidrato.

En al menos una realización existe una composiciOn que contiene bromhidrato de
bupropion y al menos un excipiente farmacØuticamente aceptable, en donde la
administración de una cantidad (por ejemplo, aproximadamente 100 mg/kg) de
15 bromhidrato de bupropion a una primera rata da como resultado una menor incidencia de
crisis convulsivas y/o crisis convulsivas inducidas por bupropion menos graves cuando se
las compara con la incidencia y/o gravedad de las crisis convulsivas inducidas por
bupropion como resultado de la administración de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata, en donde el bromhidrato de bupropion que
20 es administrado a la primera rata proviene de otra fuente diferente que la composición (es
decir, ci bromhidrato de bupropion que se administra a la primera rata no se extrae de la composición); en donde el bromhidrato de bupropion que se administra a la primera rata
puede ser de la misma forma que la sal bromhidrato de bupropion que estÆ en la
composición y en donde la incidencia y/o gravedad de las crisis convulsivas inducidas
1025 por bupropion son medidas por medio de un electroencefalograma utilizando un
electrodo profundo implantado en el hipocampo.

Los ejemplos a continuación no son limitantes y son representativos de diversos aspectos
de algunas realizaciones de la presente invenciOn.

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EJEMPLOS

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EJEMPLO 1: PREPARACION DE LA SAL BROMHIDRATO DE BUPROPJON

La sal de bupropion HBr se preparó de acuerdo con ci mØtodo que se muestra en el
esquema 1:
5
Esquema 1

3rcIoropopiofnona
PM= 1686Z

ReacciOn de bcotnación

Br2

CH2C12 CLQJL1
2 -brorno-3’-clorn-p ropiafenona
PM = 247,52
Reacdón de aminackSn

yBr CH2Cl2 HN CI

t-butiianna

2-t-butllamino-3-cioro-propiofenona
PM= 239,75
PurffIcaciOn/ Predpitac.iOiil Secado
0 0

1) purificación, tolueno

HN

C(CH 2) precipitacion:

’ LJ

IPA, gas HBr C(CH3)3
3) secadlu BupopionHBr
Inteimediarlo

Etapa de fiuializaciOn

BupropioaHBr Taniizado. Bupropionl{Br
Intermediarlo Envasado Libei’ac:iOn final

(a) Reacciones de bromaciOn y condensación
10 El material de partida 3 ’-cloro-propiofenona se bromó en cloruro de metileno por goteo de bj-omo en condiciones controladas. Al terminar la reacciOn se purificó el licor mache y despues se realizó la segunda reacción transfiriendo la solución del derivado bromado a la terc-butilamina. La segunda reacción de sustitución (el grupo amino de la tere-butilainina sustituye al Ætomo de bromo)forma la molØcula final de bupropion. DespuØs 15 de la purificaciOn del licor mache se obtuvo una soluciOn de bupropion en tolueno. Se evaporó el disolvente y el bupropion se disolvió en isopropanol. Se precipitó el bromhidrato de la soluciOn de isopropanol, con bromuro de hidrógeno gaseoso. Al

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terminar la precipitación, el producto se centrifugó, se lavó con isopropanol y se secó al vaclo. Tras la aprobación de la descarga del secador, se descargó en tambores Kraft
dentro de bolsas dobles de polietileno.
En ci paso final, el intermediario anterior se tamizO para obtener ci producto final que se
5 empacó en tambores Kraft dentro de bolsas dobies de polietileno.
El anÆlisiselemental del bupropion HBr se realizO con un analizador elemental Fisons
EA 1108. Los resultados fueron compatibles con la fOrmula molecular del bupropion

HBr.

10 EJEMPLO 2: COMPRIMIDOS DE BUPROPION HBr DE LIBERACION
EXTENDIDA (XL)
El objetivo de este ejemplo fue describir ci desarrollo de bupropion HBr XL (174 y 348
mg). Los procedimientos de granulación, formaciOn de comprimidos y recubrimiento se describen detalladamente en este ej emplo. Se realizaron pruebas in vitro sobre los
15 nUcleos, los nücleos recubiertos con etilcelulosa y los comprimidos con ci recubrimiento
final para determinar quØ formulación daba los resultados deseados.
A partir de sus formulas estructurales, se observa que la diferencia entre las sales de bupropion HC1 y bupropion HBr es la sal. Esto, por supuesto, produce un peso molecular diferente. Sin embargo, estas diferencias Se tomaron en cuenta en el presente estudio y se
20 hicieron modificaciones a fin de obtener resultados de correlación in vitro con ci
bupropion HC1 usando estudios de disoluciOn.
Se observó previamente que cuando se analizó la liberaciOn de 150 mg de bupropion
HC1, ci valor de base que se liberó fue de 130 mg. Sin embargo, cuando se analizaron
150 rug de bupropion HBr, el valor de base liberado fue solo de 112 rug. Dc manera que
025 se tuvo que aumentar la cantidad de bupropion HBr para aumentar ci valor de base de
112 rug a 130 mg, que era el valor de referencia. Los estudios mostraron que 174 mg de bupropion HBr liberaban un valor de base de 130 mg y por esta razón se usaron 174 mg
en lugar de 150 mg de bupropion HBr.
Bupropion HBr XL - Pràceso de granuiación
30 En la Figura 1 se muestra un resumen del proceso de fabricación usado para la
preparaciOn de comprimidos de bupropion HBr XL.
Se usaron los siguientes materiales en la granulación de los nücieos de liberación
inmediata de los comprimidos de bupropion HBr EA: bupropion HBr, alcohol polivinIlico (PVA) y agua purificada. Una vez granuiado, se agregó lubricante
35 (COMPRITOL9888) para completar la formulaciOn.

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Cada ensayo se dividió en 5 partes. El porcentaje de IFA en cada formuiación fue de 93,75%; el porcentaje de PVA en cada formulación fue de 3,125%. En la Tabla 1 se describe un resumen del desgiose de cada ensayo por parte.
El PVA se disolvió en agua purificada mediante un agitador magnØtico y se preparó una
5 soiución transparente e incolora.
Para granular ci bupropion HBr en grÆnulosse usó el equipo de leeho fluido NIRO con la solución en PVA en un proceso conocido corno amasado hümedo. La Figura 2 presenta
un resumen del procedimiento de granulación.
El bupropion HBr se cargo en el lecho fluido y se inició la granulaciOn. Las
10 especificaciones usadas como pautas se muestran en la Tabla 2.
Se determinó la pØrdida por secado despuØs de cada granulación con el analizador de
humedad. Se tomó ilna muestra de 1 g y se cargO en el analizador de humedad. La
muestra se analizó durante 5 minutos a una temperatura de 105°C.
SDespuØs de completar la granulación de cada parte del lote, se cornbinaron las cinco
15 partes. Se tamizaron a mano con un tarniz de malla n° 14 (1,4 mm) y todos los granos
mÆs grandesse pasaron a travØs del Comil equipado con un tarniz de 2 mm.
Se usó COMPRITOL fi 888 corno lubricante en la forrnulaciOn. Los grÆnulos de
bupropion HBr tamizados y ci COMPRITOLfi 888 se cargaron en el mezelador en V y
se mezclaron durante 5 minutos. El COMPRITOLfi 888 constituyO 3,125% de la
20 formulación. El tamaæo del lote final de grÆnulosse describe en la Tabla 3.
Bupropion HBr XL - Proceso de forrnación de comprimidos
Para preparar los comprimidos de bupropion HBr se usó la compresora Beta. Segün la
dosis del comprimido, 174 mg o 348 mg, se usaron diferentes juegos de punzones. Se
usaron los punzones de 7 mm para comprimir los comprimidos de 174 mg y los punzones
25 de 9 mm y 10 mm para comprimir los comprimidos de 348 mg. Los punzones se
pulieron antes de cada ciclo.
Se determinó que los pesos de los comprimidos eran 185,6 mg para los comprimidos de
174 mg de dosis y 371,2 mg para los comprimidos de 348 mg de dosis. Se hicieron estos ajustes en el peso del comprirnido para compensar el hecho de que se estaba usando
30 bupropion HBr en lugar de bupropion HC1. Los pesos de los comprimidos individuales
tuvieron un lirnite de control de – 5%, y el peso promedio de los comprimidos tuvo un
ilmite de control de – 3% (usando diez comprimidos).
Se usó un durórnetro para determinar la fuerza necesaria para romper diametralmente los comprimidos (fuerza de rotura por cornpresión) en dos mitades iguales. Un intervalo
35 predeterminado, entre 6,0 y 12,0 SC, estableciO las especificaciones de dureza para los
comprimidos de 174 mg y 348 rng,

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La friabilidad se determinó usando comprimidos que tenian en total un peso de 6,5 g en
un friabilómetro durante 4 minutos a 25 rpm. Los comprimidos se desempolvaron antes
y despuØs de la prueba. Se usó como criterio una pØrdida de peso menor que 0,8% a fin
de aceptar o rechazar el lote.
5 La Tabla 4 resume las especificaciones del ajuste de la compresora de comprimidos.
Para todos los lotes se mantuvieron las especificaciones dentro del intervalo y en el ajuste asignado.
La Tabla 5 resume las especificaciones que se mantuvieron constantes durante la
compresión de todos los lotes.
10 El diagrama de flujo que se muestra en la Figura 2 describe los pasos previos e incluye el
proceso de formación de comprimidos. La Figura 3 presenta un resumen del
procedimiento de formación de comprimidos.
Bupropion HBr XL - Proceso de recubrimiento

it En la Figura 4 se muestra un resumen del proceso de recubrimiento usado para el
15 recubrimiento de comprimidos XL de bupropion HBr. El primer recubrimiento es de
etilcelulosa (por ejemplo, ETHOCELfi) que controla la liberación, al que sigue un recubrimiento final que actüa como barrera contra la humedad.
Para el recubrimiento de etilcelulosa y el recubrimiento final de los comprimidos XL de bupropion HBr, se usó el sistema O’Hara Labcoat II de 15 pulgadas. TambiØn se usaron
20 una boquilla de pulverización y un mezclador de hØlice anexos.
Se desarrollaron varias soluciones de recubrimiento de etilcelulosa que se usaron para
recubrir los comprimidos de bupropion HBr. La capa de recubrimiento de etilcelulosa se
eolocó sobre los comprimidos que contenlan una de las forinulaciones que aparecen en la
Tabla 6.

025 En ía formulación 1, se combinaron alcohol etflico al 95% y AlP a! 99% en un recipiente
de acero inoxidable. Mientras se agitaba se agregó PEG 4000 y se permitió que se
disolviera. Una vez disuelto, se agregó etilcelulosa (por ejemplo, ETHOCELfi) y se dejó
en agitación durante 30 minutos. DespuØs, se agregó povidona a la solución y se mezcló
durante toda la noche (15 a 20 horas).
30 En la formulacióri 2, se colocó PEG 4000 en un vaso de laboratorio con sebacato de
dibutilo y se agitó hasta que se disolvieron. Se agregó alcohol etIlico como corresponde
para permitir la disolución completa del PEG 4000. En un recipiente de acero inoxidable distinto se colocO el resto del alcohol etIlico al 95% y se agregO la etilcelulosa con
agitación y se agitó durante 30 minutos. A continuación, se agregó povidona y se dejó en
35 agitación durante toda la noche (15 a 20 horas).
En la formulación 3, se colocó alcohol etilico a! 95% en un recipiente de acero
inoxidable. Mientras se agitaba se agregó PEG 4000 y se permitió que se disolviera.

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Una vez disuelto, se agregó la etilcelulosa y se dejó en agitación durante 30 minutos. DespuØs, se agregO povidona a la solución y se rnezciO durante toda la noche (15 a 20 horas).
Se desarrollaron dos soluciones de recubrimiento final y se usaron para recubrir los
5 comprimidos de bupropion HBr despuØs que habfan sido recubiertos primero con el
recubrimiento de etilcelulosa.
Una de las formulaciones siguientes que se muestran en la Tabla 7 se usó para recubrir
los comprimidos con un recubrimiento final.
En la forrnuiación A, se coiocó el agua purificada en un vaso de vidrio de iaboratorio y se
10 le agregó Chroma-Tone DEB 5156-CLE y se dejó que se mezclara durante 15 minutos.
El EUDRAGIT fi se paso a travØs de un tarniz de malia 60) antes de usar. DespuØs
de esto, se agregO ci EUDRAGITfi al vaso de!aboratorio y se agitó durante 15 minutos

mÆs.

En la formulaciOn B, se colocO la parte 1 del agua purificada en un vaso de vidrio de
15 laboratorio y se le agregó PEG 4000 y se dejO que se mezclara hasta que se disoiviO
totaimente (5 minutos). DespuØs se agregó citrato de trietilo y se dejó que se mezclara durante otros 5 minutos. Una vez disuelto, se agregó la soiución a la suspension de EUDRAGITfi y se dejó en agitaciOn durante 45 minutos. El EUDRAGIT fi se paso a
travØs de un tarniz de maila (0 60) antes de usar. En otro vaso, se agregó la parte 2 del
20 agua purificada al SYLOIDfi 244FP y se mezciO hasta que se disolviO por compieto (10
minutos). Finaimente, la suspension de SYLOIDfi se agregó a la suspension de EUDRAGITfi y se dejó en agitación durante otros 10 minutos.
La Tabla 8 resume las especificaciones que se controiaron en ci proceso de recubrimiento
de etiliceluiosa y sus intervajos.
25 La Tabla 9 resume las especificaciones que se controlaron en ci proceso de recubrimiento
final y sus intervalos.
Estudios in vitro sobre los nücleos de bupropion HBr
Se realizó la prueba de disoiuciOn a los nücleos de bupropion HBr, a los diferentes
aurnentos de peso de los nücieos recubiertos con etilcelulosa y a los diferentes aumentos
30 de peso de los comprimidos recubiertos con el recubrimiento final. Se utilizó ci mØtodo
USP-1 para realizar estos estudios. Se realizO la prueba de disolución utilizando 900mL
de HC1 0,1N a una velocidad de 75rpm. Las muestras se tomaron cada hora durante 16 horas. Los perfiles de disoluciOn se obtuvieron graficando ci porcentaje acumulado de
IFA disuelto en función de los tiempos de muestreo. Se mantuvieron las condiciones de
35 sedimentacjOn durante todos los experimentos.
En varios ensayos se utilizO ci mØtodo USP-3 para realizar los estudios de disoluciOn.
Estas pruebas de disoluciOn se realizaron durante 16 horas en total con ci siguiente

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desgiose: 2 horas utilizando 900mL de Fluido gÆstricosimulado (SGF) a pH 1,2 con
0,5% de laurilsulfato de sodio (SLS), seguido de 2 horas en 900mL de buffer acetato a
pH of 4,5, seguido de 12 horas en 900mL de Fluido intestinal simulado en buffer fosfato (SIF) a pH 6,8. Estos resultados Se graficaron con los datos in vivo y los datos del
5 Bupropion HC1 a fin de realizar una comparación.
Estudio sobre el lote BUP-HBr-XL-009-5
La formulación se granuló usando un equipo de lecho fluido NIRO. DespuØs de terminar
la granulación, ci lote se tamizó y antes de comprimir se agregó el lubricante (COMPRITOLfi 888). La mezcla final se coinprimió en forma de comprimidos de 348
10 mg con la compresora Beta con los punzones estÆndar redondos cóncavos de 9 mm y 10
mm. La Tabla 10 describe la cantidad de cada material en la granulación de los
comprimidos de 348 mg. Se hizo un primer ciclo de compresión para producir
comprimidos con diferentes valores de dureza a fin de determinar los efectos de la
dureza, silos hubiera, sobre la disolución (Figura 5). Se realizó una prueba de disolución
15 a los nücleos de 348 mg a fin de determinar su liberación (Figura 6).
Los resultados de la granulacion muestran que el tiempo de granulación promedio es de
2,0 horas y la LOD (pØrdida por secado) promedio en % es de 0,345%. Las Tablas 11 y
12 resumen los valores teOricos y reales de los parÆmetros que se controlaron en el
proceso de compresión usando los punzones de 9 mm y 10 mm, respectivamente.
20 A fin de determinar la dureza de los comprimidos para este estudio, se comprimieron
comprimidos con diferentes valores de dureza y se les realizó la prueba de disolución
para ver la diferencia.
Se comprimieron comprimidos con durezas de 4 kp, 6 a 7 kp y 9 a 10 kp cuyos perfiles
de disolución se muestran en la Figura 5. Se observó que no hubo una diferencia
025 significativa entre los tres intervalos de dureza diferentes.
Los perfiles de disolución de los nücleos de 348 mg (Figura 6) y 174 mg (Figura 7) mostraron que los nücleos liberaron aproximadamente el 100 por ciento del IFA en una hora.

La disolución de los nücleos de 10 mm y 348 mg tambiØn se llevó a cabo para ver si la
30 liberación de estos comprimidos era mÆs rÆpida encomparación con la de los niicleos de
9 mm debido a su mayor area superficial (Figura 7).
Cuando se compararon los resultados de disoluciOn de los nücleos de 9 mm y 10 mm (Figura 8), los nócIeos de 10 mm no mostraron diferencias con respecto a los nücleos de
9 mm. Por lo tanto, los nIic1eos de 10 mm no se fabricaron ni se usaron mÆs en este
35 estudio.
Estudio sobre el lote BUP-HBr-XL-021-5

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La formulación se granuló usando un equipo de lecho fluido NIRO. La mezela final se cornprimió en forma de comprimidos de 174 mg usando la compresora Beta con los punzones estÆndar, redondos ycóncavos de 7 mm de acero inoxidable. La Tabla 13 describe la cantidad de cada material en la granulación de los comprimidos de 174 mg.
5 Es de destacar que los comprimidos de 348 y 174 mg tuvieron la misma composición y
cantidad de cada material; la ünica variación fue el peso del comprimido, que se ajustó en
la etapa de compresión. Se realizó una prueba de disolución a los nücleos de 174 mg
para observar su iiberación (Figura 9).
Los resultados de la granulación muestran que ci tiempo de granulación promedio es de 2
10 horas con 6 minutos y la LOD promedio en % es de 0,26%. La Tabla 14 resume los
valores teóricos y reales de los parÆmetrosque se controlaron en ci proceso de
compresión usando los punzones de 7 mm.
El perfil de disolución de los nücleos de 174 mg (Figura 9) mostró que los nücleos
liberaron aproximadamente ci 100 por ciento del IFA en una hora.
15 Estudio sobre el lote BUP-HBr-XL-348 mg-013-5
Usando los comprimidos de 348 mg, se pulverizó un recubrimiento de etilcelulosa (por ejemplo ETHOCELfi 0 "EC") seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento O’Hara Labcoat II.
Los materiales usados en recubrimiento de etilcelulosa, su contribución porcentual al
20 total de la solución, la cantidad de cada uno en ci lote y ci porcentaje de los sólidos en la
solución se presentan en la labia 15.
Los parÆrnetros son lossiguientes: velocidad de puiverización: 13 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50°C; temperatura del producto: 35°C – 5°C; y
Suministro de flujo de aire: 200 CFW.
25 Llevó 2 horas y 25 minutos recubrir los comprimidos con un aumento de peso de 32 mg.
Se determinaron y se registraron en la Tabla 16 los pesos de los comprimidos a los 28
mg, 30 mg, 32 mg y 34 mg de aumento de peso.
El perfil de disolución (Figura 10) muestra que los comprimidos con un aumento de peso
de 34 mg de recubrimiento de etilcelulosa liberaron bupropion HBr mÆslentamente que
30 los demÆsy que los comprimidos con un aumento de peso de 28 mg fueron los mªs
rÆpidospara liberar ci bupropion HBr en comparación con los otros aurnentos de peso.
Los materiales usados en ci recubrimiento final, su contribución porcentual al total de la solución, la cantidad de cada uno en ci lote, la cantidad de contribución de sólidos en
gramos y ci porcentaje de los sOlidos en la soluciOn se presentan en la Tabla 17.
35 Los parÆmetros son los siguientes:velocidad de pulverizaciOn: 6 g/min; velocidad de la
paiia: 12,0 rpm; aire de entrada: 40°C; temperatura del producto: 35°C – 5°C; y
Suministro de flujo de aire: 200 CFW.

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DespuØs de este ciclo del ensayo, no se volvió a usar Chroma-Tone debido a los
problemas de formuiación que causó. En primer lugar, limitaba la composiciOn de la formulaciOn debido a su falta de flexibilidad porque que no se podlan variar las
proporciones de SYLOIDfi, PEG y citrato de trietilo. En segundo lugar, la soluciOn hacla
5 espuma y coagulaba, lo que a su vez hacla que se tuviera que cambiar el proceso de
preparación de la soiución de recubrimiento con respecto al original para que no voiviera
a coagular. Sin embargo, aün se puede considerar el Chroma-Tone como una opcion para
la formulación pero se deberÆn usardiferentes grados y hacer mezclas diferentes para adecuarse a los comprimidos de bupropion HBr XL.
10 Llevó 31 minutos agregar 7 mg de aumento de peso de la solución de recubrimiento final
a los comprimidos.
Se determinaron y se registraron en la Tabla 18 los pesos de los comprimidos a los 4 mg,
5 mg, 6 mg y 7 mg de aumento de peso.
El perfil de disolución (Figura 11) muestra que los comprimidos con un aumento de peso
15 de 7 mg de recubrimiento final fueron los de liberación mÆslenta en comparación con los
otros dos aumentos de peso (5 mg y 6 mg de aumento de peso).
Estudio sobre el lote BUP-HBr-XL-348 mg-0 18-5
Usando los comprimidos de 348 mg, se puiverizó un recubrimiento de etilcelulosa
seguido de un recubrimiento final sobre los comprimidos, con ci equipo de recubrimiento
20 O’Hara Labcoat II.

Los materiales usados en el recubrimiento de etilcelulosa (por ejemplo, ETHOCELfi), su contribución porcentual al total de la soluciOn, la cantidad de cada uno en el lote y el porcentaje de los sólidos en la solución se presentan en la Tabla 19.
Los parÆmetrosson los siguientes: velocidad de pulverización: 13 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50°C; temperatura del producto: 35°C + 5°C; y
Suministro de flujo de aire: 200 CFW.
El proceso de recubrimiento de este ensayo demoró 2 horas y 13 minutos en lograr un aumento de peso de 32 mg. Se determinaron y se registraron en la Tabla 20 los pesos de
los comprimidos a los 26 mg, 28 rug, 30 mg y 32 mg de aumento de peso.
30 La Figura 12 muestra que la velocidad de liberación de los comprimidos con aumentos de
peso de 30 mg y 32 mg de recubrimiento con etilcelulosa fue casi la misma. La
liberaciOn de los comprimidos con un aumento de peso de 32 mg fue mÆs lentaque la de
los comprimidos con 30 mg de aumento de peso en las primeras 5 horas de disolución. DespuØs de 6 horas, la liberación de los comprimidos con un aumento de peso de 32 rug
35 fue ligeramente mÆs rÆpidaque la de los de 30 mg de aumento de peso. El factor de
similitud f2 confirmó que la velocidad de liberación de los dos aumentos de peso fue
similar (91,32%).

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Los materiales usados en el recubrimiento final, su contribución porcentual al total de la solución, la cantidad de cada uno en el lote, la cantidad de contribución de sólidos en
gramos y el poreentaje de los sólidos en la solución se presentan en la Tabla 21.
Los parÆmetros son los siguientes: velocidad de pulverización: 6 g/min; velocidad de la
5 paila: 12,0 rpm; aire de entrada: 40°C; temperatura del producto: 35°C – 5°C; y
suministro de flujo de aire: 200 CFW.
Llevó 41 minutos agregar 7 mg de aumento de peso de la soluciOn de recubrimiento final
a los comprimidos. Se detenninaron y Se registraron en la Tabla 22 los pesos de los comprimidos a los 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso.
10 La Figura 13 muestra el perfil de liberación de los comprimidos con 7 mg de aumento de
peso de recubrimiento final.
Estudio sobre el lote BUP-HBr-XL-174 mg-022-5
Usando los comprimidos de 174 mg, se pulverizO un recubrimiento de etilcelulosa
seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento
15 O’Hara Labcoat II.

Los materiales usados en el recubrimiento de etilcelulosa (por ejemplo, ETHOCELfi), su contribución porcentual al total de la solución, la cantidad de cada uno en el lote y ci porcentaje de los sOlidos en la solución se presentan en la Tabla 23.
Los parametros son los siguientes: velocidad de pulverizaciOn: 13 g/min; velocidad de la
20 paila: 12,0 rpm; aire de entrada: 50°C; temperatura del producto: 35°C – 5°C; y
suministro de flujo de aire: 200 CFW.
LlevO 4 horas y 30 minutos agregar 30 mg de aumento de peso de la soluciOn de
recubrimiento de etilcelulosa a los comprimidos. Se determinaron los pesos de los
. comprimidos a los 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 29 mg y 30 mg de aumento de
25 peso y se registraron en la Tabla 24.
La Figura 14 muestra el % disuelto de cada una de las muestras con diferentes aumentos
de peso por el recubrimiento de etilcelulosa (22 mg, 24 mg, 28 mg y 30 mg de aumento
de peso). A partir de la grÆfica,resultó evidente que la liberación de los comprimidos
con un aumento de peso de 30 mg de recubrimiento de etilcelulosa fue mÆslenta que la
30 los otros aumentos de peso. Cuando se compararon las velocidades de liberaciOn de los
comprimidos con aumentos de peso de 30 mg y 28 mg, solo se observó una pequefla diferencia en la liberaciOn. El factor de similitud f2 confirmO la similitud de las dos liberaciones (92,34%).
Los materiales usados en ci recubrimiento final, su contribución porcentual al total de la
35 soluciOn, la cantidad de cada uno en el lote, la cantidad de contribuciOn de sólidos en
gramos y el porcentaje de los sóiidos en la solución se presentan en la Tabla 25.

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Los parmetros son los siguientes: velocidad de pulverización: 6 g/min; ’velocidad de la paila: 12,0 rpm; aire de entrada: 40°C; temperatura del producto: 35°C – 5°C; y Suministro de flujo de aire: 200 CFW.
Llevó 1 hora y 26 minutos agregar 7 mg de aumento de peso de la solución de
recubrimiento final a los comprimidos. Se determinaron y se registraron en la Tabla 26
los pesos de los comprimidos a los 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso.
El perfil de disolución (Figura 15) muestra que los comprimidos con un aumento de peso
de 7 mg de recubrimiento final fueron los de liberación mÆslenta en comparación con los
de 5 mg y 6 mg de aumento de peso.
10 Estudio sobre el lote BUP-HBr-XL-348 mg-023-5
Usando los comprimidos de 348 mg, se pulverizO un recubrimiento de etilcelulosa sobre
los comprimidos, con ci equipo de recubrimiento O’Hara Labcoat IL
Los materiales usados en el recubrimiento de etilcelulosa (por ejemplo, ETHOCELfi), su contribución porcentual al total de la solución, la cantidad de cada uno en el lote y el
15 porcentaje de los sólidos en la solución se presentan en la Tabla 27.
Los parÆmetros sonlos siguientes: velocidad de pulverización: 13 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50°C; temperatura del producto: 35°C + 5°C; y
Suministro de flujo de aire: 200 CFW.
Llevó 2 horas y 16 minutos agregar 32 mg de aumento de peso de la solución de
20 recubrimiento de etilcelulosa a los comprimidos. Se determinaron los pesos de los
comprimidos a los 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso y se registraron en
la Tabla 28.

El perfil de disolución (Figura 16) muestra que los comprimidos con un aumento de peso
de 32 rng de recubrimiento de etilcelulosa cuando se los comparó con los comprimidos
025 con un aumento de peso de 26 mg, 28 mg, y 30 mg de recubrimiento de etilcelulosa
fueron los de liberación mÆs lenta.
Estudio sobre ci lote BUP-HBr-XL-348 mg-025-5
Usando los comprimidos de 348 mg, se pulverizó un recubrimiento de etilcelulosa
seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento
30 O’Hara Labcoat II.

Los materiales usados en ci recubrimiento de etilcelulosa (por ejemplo, ETHOCELfi o
EC), su contribución porcentual al total de la soluciOn, la cantidad de cada uno en el lote
y el porcentaje de los sólidos en la solución Se presentan en la Tabla 29.
Los parÆmetros son los siguientes: velocidad de pulverización: 13 g/min; velocidad de la
35 paila: 12,0 rpm; aire de entrada: 50°C; temperatura del producto: 35°C – 5°C; y
suministro de flujo de aire: 200 CFW.

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Llevó 2 horas y 13 minutos agregar 32 mg de aumento de peso de la solución de recubrimiento de etilcelulosa a los comprimidos. Se determinaron los pesos de los comprimidos a los 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso y se registraron en

la Tabla 30.

5 El perfil de disolución (Figura 17) muestra que los comprimidos con un aumento de peso
de 32 mg de recubrimiento de etilcelulosa cuando se los comparó con los de un aumento
de peso de 26 mg fueron los de liberación mÆs lenta al comienzo y mªs rÆpida alas 7
horas. Cuando se compararon los comprimidos con un aumento de peso de 32 mg de recubrimiento de EC con los de un aumento de peso 30 mg de recubrimiento de
10 etilcelulosa, la liberación de los comprimidos con un aumento de peso de 32 mg fue mÆs
lenta hasta las 10 horas. El factor de similitud –2 mostrO que la Jiberación de los comprimidos con aumentos de peso de 30 mg y 32 mg fue de hecho similar (93,72%).
Los materiales usados en ci recubrimiento final, su eontribuciOn poreentual al total de la solución, la cantidad de cada uno en el lote, la cantidad de contribución de sólidos en
15 gramos y el porcentaje de los sólidos en la solución se presentan en la Tabla 31.
Los parªmetros son los siguientes: velocidad de pulverización: 6 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 40°C; temperatura del producto: 35°C – 5°C; y
Suministro de flujo de aire: 200 CFW.
Se alteró la solución de recubrimiento para este lote cambiando el porcentaje de sólidos
20 de cada componente sólido de la solución. El porcentaje de contribución de sólidos de
EUDRAGITfi se redujode 65% a 56,5%. El porcentaje de SYLOIDfi, CARBOWAXfi
y citrato de trietilo se aumentaron de 25%, 6,65% y 3,39% a 30%, 9% y 4,5%,
respectivamente.
,Llevó 40 minutos agregar 7 mg de aumento de peso de la solución de recubrimiento final
5 a los comprimidos. Se determinaron y Se registraron (Tabla 32) los pesos de los
comprimidos a los 4 rng, 5 mg, 6 mg y 7 mg de aumento de peso.
El perfil de disolución (Figura 18) muestra que los comprimidos con un aumento de peso
de 7 mg fueron los de liberación mÆs lenta de las tres muestras probadas. Sin embargo, el cÆlculode –2 mostró que la liberación de los comprimidos con un aumento de peso de 6
30 mg fue similar a la de los de un aumento de peso de 7 mg de recubrimiento final
(93,33%).
Estudio sobre ci lote I3UP-HBr-XL-348 mg-026-5
Usando los comprimidos de 348 mg, se pulverizO un recubrimiento de etilcelulosa sobre
los comprimidos, con ci equipo de recubrimiento O’Hara Labcoat II.
35 Los materiales usados en el recubrimiento de etilcelulosa (pot ejemplo, ETHOCELfi o
EC), su contribución porcentual al total de la solución, la cantidad de cada uno en el lote
y el porcentaje de los sólidos en la solución se presentan en la Tabla 33.

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Los parÆmetrosson los siguientes: velocidad de pulverización: 13 g/min; velocidad de la paila: 12,0 rpm; aire de entrada. 50°C; temperatura del producto: 35°C + 5°C; y
Suministro de flujo de aire: 200 CFW.
Llevó 2 horas y 11 minutos agregar 32 mg de aumento de peso de la solución de
5 recubrimiento de etilcelulosa a los comprimidos. Se determinaron los pesos de los
comprimidos a los 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso y se registraron en
la Tabla 34.

El perfil de disolución (Figura 19) muestra que los comprimidos con un aumento de peso
de 32 mg de recubrimiento de etilcelulosa fueron los de liberaciOn mÆs lenta en
10 comparaciOn con las otras tres muestras con menores aumentos de peso de recubrimiento
de etilcelulosa (26 tug, 28 mg y 30 mg de aumento de peso).
Estudio sobre el lote BUP-HBr-XL-174 mg-027-5
Usando los comprimidos de 174 mg, se pulverizó un recubrimiento de etilcelulosa
seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento
15 O’Hara Labcoat II.
Los materiales usados en el recubrimiento de etilcelulosa (por ejemplo, ETHOCELfi o
EC), su contribución porcentual al total de la solución, la cantidad de cada uno en el lote
y el porcentaje de los sólidos en la solución se presentan en la Tabla 35.
Los parÆmetros son lossiguientes: velocidad de pulverización: 13 g/min; velocidad de la
20 paila: 12,0 rpm; aire de entrada: 50°C; temperatura del producto: 35°C – 5°C; y
Suministro de flujo de aire: 200 CFW.
Llevó 3 horas y 29 minutos agregar 32 mg de aumento de peso de la solución de recubrimiento de etilcelulosa a los comprimidos. Se detenninaron los pesos de los comprimidos a los 22 mg, 24 mg y 26 mg de aumento de peso y se registraron en la Tabla

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El perfil de disolución (Figura 20) muestra que los comprimidos con un aumento de peso
de 26 mg de recubrimiento de etilcelulosa fueron los de liberación mÆs lenta de las tres muestras probadas.
Los materiales usados en ci recubrimiento final, su contribuciOn porcentual al total de la
30 solución, la cantidad de cada uno en el lote, la cantidad de contribuciOn de sólidos en
gramos y el porcentaje de los sólidos en la solución se presentan en la Tabla 37.
Los parmetros son los siguientes: velocidad de pulverización: 6 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 40°C; temperatura del producto: 35°C + 5°C; y
Suministro de flujo de aire: 200 CFW.
35 Llevó 1 hora y 17 minutos agregar 7 mg de aumento de peso de la solución de
recubrimiento final a los comprimidos. Se determinaron y se registraron, en la Tabla 38
los pesos de los comprimidos a los 4 mg, 5 mg, 6 tug y 7 mg de aumento de peso.

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El perfil de disolución (Figura 21) muestra que los comprimidos con un aurnento de peso
de 7 mg de recubrimiento final fueron los de iiberación mÆslenta al comienzo en
cornparaeión con los de 4 rng, 5 mg y 6 mg de aumento de peso. Sin embargo, aproximadamente a las 12 horas la liberación de las 4 muestras era similar.

EJEMPLO 3: EVALUACION DE CLORHIDRATO DE J3UPROPION Y BROMHIDRATO DE BUPROPION A DOSIS CONVULSIVAS Y NO CONVULSIVAS EN UN EEG CORTICAL EN RATONES
Se llevó a cabo inicialmente un estudio conductual a fin de evaluar las actividades

proconvulsivas en ratones CD-i comparando el clorhidrato de bupropion y el bromhidrato de bupropion. Los estudios demostraron que las crisis convulsivas en ratones eran rnÆs graves conci clorhidrato de bupropion que con el bromhidrato de bupropion. Sin embargo, estos estudios estaban limitados a las diferencias conductuales observables entre las dos formas de la sal de bupropion y no median las diferencias no observables (por ejemplo, la actividad electroencefalografica). Por lo tanto, se utilizó el EEG para estudiar el efecto inductor de crisis convulsivas de estos fÆrrnacosy cuantificar los efectos en el EEG del clorhidrato de bupropion y bromhidrato de bupropion en diferentes intervalos de dosis.

El estudio evaluó los efectos en ci encefalograrna (EEG) cortical de ratones producido por el clorhidrato de bupropion y el bromhidrato de bupropion a cinco dosis en el intervalo de 100-150 mg/kg. Se llevó a cabo una comparación de los efectos de las dosis equimolares de las sales clorhidrato de bupropion y bromhidrato de bupropion mediante

EEG en los ratones.

Sistema de prueba: para este estudio se utilizaron 30 ratones hembra sanos CD-1, con un peso corporal de 25-29 g que se aclimataron en un periodo minimo de 4 dIas. Luego de la distribución en grupos, se identificO a cada animal mediante una marca en la superficie dorsal de la cola. Las condiciones ambientales inclulan una temperatura de 22–3°C e iluminación artificial en un ciclo de 12 horas de luz/oscuridad. Actividades de rutina tales como limpieza, alimentación y surninistro de agua fueron realizadas siguiendo el protocolo actual SOPS de RCS1.
El diluyente usado fue cioruro de sodio al 0,9%. La temperatura de almacenarniento fue de aproximadarnente 25°C. Se agregO la cantidad adecuada de sal de bupropion (clorhidrato de bupropion o bromhidrato de bupropion) a la solución de cloruro de sodio al 0,9% para obtener la concentración deseada.

Compuesto de Dosis Cantidad de saljVolumen de Volumen de la prueba (mg/kg de peso (g) la soluciOn dosis

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corporal) sauna (mL) (mL/kg)
Clorhidrato de 100 0,05 5 10
bupropion
Clorhidratode 125 0,0625 5 10
bupropion
Clorhidratode 150 0,075 5 10
bupropion

Compuesto de Dosis Cantidad de sal Volumen de Volumen de la
prueba (equivalente a (g) la solución dosis
mg de la sal sauna (mL) (mL/kg)
HC1/kg de peso
corporal)
Bromhidratode 100 0,058 5 10
bupropion
Broinhidrato de 125 0,0725 5 10
bupropion
Bromhidrato de 150 0,087 5 10
bupropion

Administración del compuesto de prueba: Se administró el compuesto de prueba por via intraperitoneal utilizando unajeringa desechable de 1 ml y una aguja de 26g. La via de administración fue intraperitoneal. Se Jes administró a los animales una uinica dosis con la excepción de aquellos que recibieron 100 mg/kg de cada sal, los cuales se volvieron a ensayar con una dosis mayor (115 mg/kg) la semana siguiente. Se ensayaron el clorhidrato de bupropion y el bromhidrato de bupropion inicialmente a 150 mg/kg a fin de ser comparados entre Si. Posteriormente se ensayaron a 125 mg/kg, 100 mg/kg y luego (n=2 cada uno) a 135 mg/kg y 115 mg/kg.
Protocolo: Los ratones habituados fueron anestesiados con isoflurano, colocados en un marco estereotÆxicoy mantenidos a temperatura normal (36-37’C) por medio de una manta homeotØrmica diseæada para ratones de retroalimentación controlada (Aparato Harvard). Bajo la anestesia con isoflurano, se realizó una incision longitudinal especializada en la linea media del crÆneo quedandoØste al descubierto. Se realizaron tres craniectomias parciales: una por encima de cada lóbulo temporal y una tercera a travØs de la region suprayacente al cortex frontal. Se fijó en cada punto un EEG craneal adaptado al tamaæo de los ratones (E363/20, electrodo con perno y tomacorriente, Plastics One Inc). Se fijO el electrodo al crªneo con cemento dental, se discontinuó la anstesia y se colocO

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al animal en la cÆrnarade registros durante 30-60 minutos luego de la recuperación.
Luego se conectaron los electrodos a un sistema de cable conector multicanal 363 con un conmutador giratorio de 6 canales SL6C y se iniciaron los registros de referencia de EEG utilizando un sistema Comet portªtil de 40 canales Digital BEG & Review System,
5 modelo Grass con BEG digital doble en tandem con un video digital continuo. Luego de
un registro de video-BEG de referencia durante 10 minutos, se inyectaron los ratones con clorhidrato de bupropion o bromhidrato de bupropion (100, 115, 125, 135 o 150 mg/kg,
i.p.). Las pruebas sobre los ratones se corrieron en paralelo de modo que el ratón con clorhidrato fue inyectado con diferencia de minutos con respecto al ratón con
10 bromhidrato y se registraron las lecturas en forma simultÆnea.Se registró un video -EEG
durante un perlodo de una (1) hora. Luego de ello, los ratones fueron regresados a sus
jaulas y luego de 24 horas se les practicó la eutanasia y se recolectaron los cerebros. AnÆlisis:Se determinó para cada ratOn la duración de las poliespigas de tipo IV de alta frecuencia (IHz) y gran amplitud (>2 X ilnea de referencia) en un perlodo de registro de

15 1 hora.

Resultados: En general, la dosis de 150 mg/kg disparó un comportamiento similar a una crisis convulsiva grave dentro de los 5 minutos de inyecciOn con cualquiera de las dos
sales. El efecto mÆs pronunciado seobservó durante los primeros minutos de registro (los primeros 15-20 minutos) pero los eventos episódicos continuaron durante toda la hora de
20 registro. Sin embargo, para los pares en estudio 1, 2 y 3, la conducta convulsiva del ratón
tratado con bromhidrato duró mÆs tiempo que en el ratón tratado con clorhidrato (en
algunos casos hasta 30 minutos mÆs).Por ejemplo, el segundo ratón tratado con
clorhidrato cesó todo tipo de conducta similar a la crisis convulsiva en aproximadamente
30 minutos luego de la inyección mientras que en el ratón tratado con bromhidrato se
25 segufan observando conductas tales como incoiporaeión y cafda, corrida con las patas
delanteras y giros a los 60 minutos.
EEG: A 150 mg/kg (n =4 por sal) el EEG no detectó prÆcticamenteninguna crisis convulsiva. Se detectaron breves (2-3 s) brotes dentro de los primeros cinco minutos
luego de la inyección que coincidió con el comienzo de una comportamiento similar a
30 una crisis convulsiva. El EEG no detectó mÆscrisis convulsivas en ning(in ratón con
ninguna de las sales luego de ese perlodo a pesar de las persistentes "conductas"
convulsivas (por ejemplo convulsiones).
Conjunto 1 1-ICI: EEG - el EEG no detectó ninguna crisis convulsiva; HBr - una Ænicay muy breve crisis convulsiva
35 Conjunto 2 HCl: EEG dos brotes muy breves detectados por EEG; I-IBr, el EEG no
detectó ninguna crisis convulsiva

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Con] unto 3 UC1: EEG - breve brote de crisis convulsiva; HBr, breve brote de crisis convulsiva detectado por, EEG
A 125 mg/kg (n = 4 por sal) el BEG registró algunas crisis convulsivas importantes. En
este caso hubo una tendencia a mÆsbrotes de crisis convulsivas en los animales inyectados con clorhidrato de bupropion. A continuación se muestra su cuantificaeión. Duración total (segundos)
Clorhidrato de bupropion

DuraciOn total (segundos)
Bromhidrato de bupropion
290 30
130 25
115 0
0 0
MEDIA= 133,8 MEDIA= 13,8
SD119,3 SD16,0
Valor P, t-test 0,093

Nümero de episodios
Clorhidrato de bupropion

Nümero de episodios
Brombidrato de bupropion
12 2
8 1
10 0
0 0
MEDIA 7,5 MEDIA 0,75
SD=5,259911 SD=0,957427
Valor P. t-test 0,045

No se captaron brotes de crisis convulsivas de tipo IV de importancia en ningün
ratón con ninguna de las sales a 100 mg/kg (n=2); 135 mg/kg (n=2); o 115 mg/kg (n2). Parece haber una pequeæa diferenciaentre las dos sales en la cantidad de brotes de crisis convulsivas detectados por EEG producidos en una dosis: 125 mg/kg. La magnitud de esta diferencia se vio comprometida por la cuarta prueba de emparej amiento porque ningün animal manifesto BEG de crisis convulsiva. Los registros de EEG cortical recogieron episodios muy breves con una dosis de 150 mg/kg pero Østos ocurrieron de la misma manera entre las sales. No se detectaron episodios de EEG de crisis convulsiva en las demÆsdosis analizadas. No se conoce la explicación de por quØ no se detectó EEG de crisis convulsiva en la dosis rnÆsalta de 150 mg/kg que causO un comportamiento convulsivo profundo. PodrIa radicar en la activación o inhibición de una ruta subcortical. Los registros de electrodo profundo podrIan revelar explicaciones para esta falta de

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resultado de EEG en la dosis de 150 mg/kg. Un punto adicional es que incluso en la
dosis de 125 mg/kg parece haber un efecto variable de las sales en el EEG. La razón para esto no estÆ clara, pero sugerimos losiguiente: (i) Variabilidad biologica in vivo simple e inherente; (ii) Un efecto de genotipo especIfico en ci ratón CD1; (iii) El uso de ratonas
5 hembras (que presentan, tal vez, episodios de ciclo estral); (iv) Peso de estudio del ratón
superior a los anteriores. Todos los ratones CD que utilizamos pesaban 25 g o mÆs,lo
que puede ser superior a lo anteriormente utilizado para anªlisis del comportarniento.
Puede haber una pequefia diferencia en EEG de crisis convuisiva eutre las dos sales de bupropion en una dosis (125 mg/kg). Sin embargo, los datos revelan que las convulsiones
10 desencadenadas por esta droga en ratones no se manifiestan cornünmente como EEG de
crisis convuisivas epileptiformes como las detectadas m.ediante electrodos colocados a
nivel cortical.

EJEMPLO 4: EVALUACION DE CLORITIDRATO DE BUPROPION
15 BROMHIDRATO DE BUPROPION PARA EFECTOS EN LA TRAZA DE EEG EN
LA RATA

Se reaiizó otra comparación de los efectos de las dosis equimolares de sales de
clorhidrato de bupropion y bromhidrato de bupropion mediante ci control de la traza de
LEG en la rata.

20 Los efectos de las dos formas salinas de bupropion, clorhidrato y brornhidrato, en la actividad del sisterna nervioso central luego de la administración intraperitoneal fueron evaluadas mediante ci control de la traza de EEG en ratas conscientes. El rnØtodo que detecta actividad electroencefalogrÆficaen ratas conscientes sigue ci descrito por
DiirmUller et al., (2000) Vigilance-Controlled Quantified EEG in Safety Pharmacology,
25 Current Protocols in Pharmacology Unit 10,6. El estudio se iievO a cabo en Porsolt &
Partners Pharmacology, Research Laboratory, Z.A. des Suhards - B.P. 9, 53940 Le Genest-Saint-Isle, Francia.
Materiales y mØtodos generales:
Sustancias: El excipiente de formulación utilzado fue solución sauna fisioiogica
30 (Laboratoire Aguettant). La sal de clorhidrato de bupropion y brornhidrato de bupropion
utilizadas fueron de Biovail Technologies (Ireland) Ltd., surninistradas como poivos
blancos y disueltas en solución sauna fisiológica. Todas las sustancias Se almacenaron en una zona seca, oscura y de acceso controlado, y se mantuvieron a temperatura ambiente controlada de 20 –3°C. Las soluciones de vehiculo se almacenaron a +4°C
35 aproximadamente. Las sustancias fueron administradas en un volumen de peso del
cuerpo de 5 ml/kg. Las dosis de clorhidrato de bupropion se expresan en mg/kg de sal.
Las dosis de bromhidrato de bupropion se expresan en mg/kg del equivalente molar de

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clorhidrato de bupropion (factor de corrección = 1,16). Las sustancias se disolvieron en solución sauna fisiológica y se prepararon frescas cada dfa de los experimentos.
Sistemas de prueba: Las ratas utilizadas fueron machos Rj: ratas Wistar (Han),
con un peso entre 280 g y 324 g aproximadamente en el momento de la implantación.
5 Fueron suministradas por Blevage Janvier, 53940 Le Genest-Saint-Isle, Francia. Las
caracterIsticas de los animales utilizados (edad, especie y raza) son comparables con los descritos en la literatura cientIfica. Al ser entregados al laboratorio, los animales se mantuvieron en grupos de un mÆximode 5, enjaulas de makrolon (44 x 28 x 19 cm) con lecho de madera (Litalabo - SPPS, 95100 Argenteuil, Francia). Los animales tenlan libre
10 acceso al alimento (Code 113 - SAFE, 89290 Augy, Francia) y agua potable. El
animalario se mantuvo con iluminación artificial (12 hs) de 7:00 a 19:00 atemperatura ambiente controlada de 21 – 3°C y humedad relativa entre 30% y 80% aproximadamente. Luego de la implantaciOn, los animales se mantuvieron individualmente enjaulas de makrolon (30 x 18 x 19 cm) en una habitación separada para animales implantados en las
15 mismas condiciones ambientales anteriores. Salvo durante las sesiones de prueba, los
animales tuvieron libre acceso a alimento (Codigo 113) y agua potable. Los animales
fueron identificados mediante una marca realizada al conector fij ado a la cabeza del
animal con un marcador indeleble. Al final del experimento las ratas se sacrificaron con
una inyección letal de pentobarbital (100 mg/kg i.p.). Los animales no fueron sometidos
20 a necropsia. No hay razón para suponer que haya habido contaminantes en el alimento,
el agua o las camas en niveles capaces de interferir con los resultados de las pruebas. No
se realizaron verificaciones para este estudio en particular.
Para la adquisición de la seflal de BEG se utilizó el software 10X2, y para el anÆlisis
visual off-line se utilizó el software ECGauto (ambos de EMKA Technologies, Francia).
4k5 Procedimiento experimental:
Procedimiento de implantación de electrodo: la cirugia de implantación Se llevó a
cabo en condiciones asØpticas. Las ratas, anestesiadas con pentobarbital de sodio (60
mg/kg i.p., mÆs dosissuplementarias de entre 5 mg/kg y 10 mg/kg aproximadamente para mantener la anestesia hasta terminar la cirugla), fueron implantadas con 2 electrodos
30 BEG de superficie, compuestos por tornillos de titanio en miniatura colocados
bilateralmente sobre la corteza fronto-parietal, y 2 electrodos de profundidad, compuestos por cables torneados de platino-iridio, colocados de forma estereothxica dentro de la zona CA3 del hipocampo (Paxinos y Watson coordina interauricular: AP +5,0 mm, L –2,5
mm, V +7,0 mm). Un tornillo adicional, colocado sobre la corteza occipital derecha,
35 sirvio de electrodo de tierra. Los electrodos se conectaron a pequeflos obturadores y toda
la unidad Se asegurO en el crÆneocon acrilato dental. Luego de la cirugla, los animales

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implantados se mantuvieron enjaulas de makrolon individuales (30 x 18 x 19 cm) y se
les dio a! menos 10 dIas para recuperarse. Se implantó un total de 27 ratas.
Equipos: para el registro de EEG, los animales se colocaron en cubiculos de
Plexiglas rectangulares (30 x 10 x 25 cm) montados sobre trotadoras. Se hicieron
5 funcionar cinco unidades de registro en paralelo. Se sujetó un conmutador giratorio sobre
el centro de cada cubiculo, unos 30 cm por encima del nivel de caminata. Por un lado, se
lo conectó al animal mediante un cable multiconductor protegido elØctricamente, y por
otro lado al sistema de condicionamiento de seflales (Coulbourn Model V75-01). Se
fijaron los filtros del sistema para todos los canales de paso alto 1 Hz y paso bajo 150 Hz,
10 respectivamente Los niveles de amplificación se mantuvieron entre 1 000x y 1 0000x. Las
seæales de EEG Sc adquirieron y procesaron en una PC (DELL 0X620-2800) instalada
con una tarj eta informÆtica(NI PCI-6023E) AD de 200kHz/12-bit de 16 canales. Esta PC
fue integrada a una red local (Ethernet) que tambiØn inc!uyó una PC para el anÆlisisde
datos, y una grabadora de CD para el almacenamiento de datos.
15 Procedimiento de anÆlisis: antes delcomienzo del procedimiento de anÆlisis,las ratas fueron habituadas en una sesión de entrenamiento de 1 hora conectÆndolasal cable
de registro y caminando en el trotador. Unos minutos antes de lanzar el primer registro,
los animales fueron transferidos de la sala de espera a la sala de pruebas, conectados al
cable de registro y colocados en el cubiculo de registro. Se inspeccionó rÆpidamente la
20 calidad de las sef&ales de EEG y se ajustaron los niveles de amplificación segiin las
necesidades. Luego se dio a los animales una sesión de registro de 1 hora sin ningün
tratamiento (control de lInea base) con intervalos de 10 minutos con ci trotador encendido (velocidad de caminata: 1,8 rn/mm) o apagado en forma alternada. Inmediatarnente
. despuØs de finalizado el registro de control de lInea base se administró a los animales
25 bromhidrato de bupropion o clorhidrato de bupropion (i.p.) y se los registró durante otra
sesión de 2 horas. 23 horas despuØs de la inyección, los animales tuvieron una sesión de
registro de 1 hora en las mismas condiciones de experimentación del dia anterior. Luego
se siguió el mismo procedimiento de registro del dIa anterior. El mismo animal se hizo
coner siempre en el mismo trotador y estuvo conectado a la misma unidad del sistema de
30 condicionamiento de seflales. Los trotadores siempre estuvieron operados con los mismos
cables de registro.
Adquisición y anÆlisis dedatos: La sefial de BEG fue digitalizada en una
frecuencia de muestreo de 500 Hz/canal de registro y los datos almacenados en archivos
de datos en bruto. El anÆlisis fuedesarrollado fuera de ifnea mediante inspección visual
35 de las trazas. Las trazas cortical y del bipocampo se mostraron individualmente para cada
rata en la pantalla de la computadora en un tiempo de resolución de 10 seg/ventana.
Luego las ventanas fueron avanzando y deteniØndose cuando una sefial mostraba una

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irregularidad y se anotaba la secuencia. Se guardaron muestras representativas de sefiales patológicas en archivos en formato pdf para presentarlas en el infornie. Se definieron
trenes de potenciales de acción o actividad de punta-onda que exceden claramente amplitudes de ilnea base y que duran al menos un segundo como actividad de crisis
5 convulsiva.
Observaciones de EEG:
Como se muestran en las Tablas 39(1)-(4) y 40(1)-(4): Se observaron episodios
aislados y poco frecuentes de EEG atipicos de carÆcter probablementeno patológico en varias ocasiones en todas las dosis. Algunos episodios fueron observados antes y despuØs
10 de la administración de la sustancia y no parecen estar directamente relacionados con la
actividad de crisis convulsiva o predispuestos a ella. Sin embargo, en 3 ratas se observó
una breve actividad de crisis convulsiva en el hipocampo, en todos los casos antes de la administración de clorhidrato de bupropion, lo que puede indicar que esas ratas eran propensas a la epilepsia. Por otro lado, a las 3 ratas se les administró sustancia el dIa
15 anterior (10, 30 y 60 mg/kg respectivamente).
En dosis de 10 mg/kg, no se observó actividad de crisis convulsiva ni en la corteza ni en
el hipocampo en ninguna rata a las que se administró clorhidrato de bupropion o bromhidrato de bupropion.
En dosis de 30 mg/kg, aparte de una rata con una breve actividad de crisis convulsiva en
20 el hipocampo durante la fase de administración previa (Fig. 22, rata Q0343, grupo HC1),
no se obsei-vó actividad de crisis convulsiva en ninguna corteza o hipocampo en ninguna
rata a las que se administró clorhidrato de bupropion o bromhidrato de bupropion.
En dosis de 60 mg/kg, aparte de una rata con una breve actividad de crisis
convulsiva en ci hipocampo durante la fase de administración previa (Fig. 23, rata
025 Q0337, grupo HC1), no se observO actividad de crisis convulsiva en ninguna corteza o
hipocampo en ninguna rata a las que se administrO clorhidrato de bupropion o
bromhidrato de bupropion.
En dosis de 100 mg/kg, se observó una rata con una breve actividad de crisis
convulsiva en el hipocampo durante la fase de administración previa. AdemÆs, las 10
30 ratas a las que se administró clorhidrato de bupropion tuvieron entre 1 y 4 crisis
convulsivas, y 4/9 ratas a las que se administró bromhidrato de bupropion tuvieron 1
crisis convulsiva (Fig. 24 A y B rata Q0348, grupo clorhidrato de bupropion; Fig. 25 A y
B rata Q0352, grupo bromhidrato de bupropion).
Las crisis convulsivas comenzaron generaimente en la corteza y fueron mªs cortas
35 en el hipocampo que en la corteza con las dos formas salinas. El retraso de inicio de la
crisis convulsiva fue muy breve para ambas formas salinas, aproximadamente 3 minutos
en promedio para la sal clorhidrato y aproximadarnente 2 minutos para la sal

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bronihidrato. La duración de la crisis convulsiva fue entre 15 y 50 segundos en la corteza. Comparado con la primera fase de crisis convulsiva, no hubo una diferencia clara en la duración de la crisis convulsiva media entre las dos formas salinas tanto, en la corteza
como en el hipocampo (Tablas 41 y 42(1)-(2)). Si se toman en cuenta las miltip1es
5 ocurrencias de crisis convulsivas, la duración global de la crisis convulsiva del grupo de
clorhidrato de bupropion fue mÆslarga que la del grupo de bromhidrato de bupropion. Control de la traza de EEG en la rata: Las figuras 22 y23 muestran trazas de 10
segundos de actividad del hipocampo. Las escalas de amplitud estân expresadas en
voltios [V]. En la figura 22 se muestra la actividad de crisis convulsiva del hipocampo de
10 aproximadamente 3 segundos de duración en la rata Q0343, y en la figura 23 se muestra
una actividad similar en la rata Q0337. Las figuras 24 A y B muestran trazas de 10
segundos de actividad de la corteza (FIG. 24A) y del hipocampo (FIG. 2413). Las escalas

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de amplitud estÆriexpresadas en voltios [V]. Se muestra la fase inicial de actividad de
crisis convulsiva tanto en la corteza como en el hipocampo en la rata Q0348. A la rata se
15 le administraron 100 mg/kg de clorhidrato de bupropion. Las figuras 25 A y 25B
muestran trazas de 10 segundos de actividad de la corteza (FIG. 25A) y del hipocampo
(FIG. 25B). Las escalas de amplitud estÆn expresadasen voltios [V]. Se muestra la fase
inicial de actividad de crisis convulsiva tanto en la corteza como en el hipocampo en la
rata Q0352. A la rata se le administraron 100 mg/kg de bromhidrato de bupropion.
20 Observaciones del comportamiento:
Como se muestran en las Tablas 39(1)-(4) y 40(1)-(4): En dosis de 10 mg/kg, no
se observó comportamiento anormal salvo en una rata en el grupo de bromhidrato de bupropion que tuvo un breve clono facial mientras estuvo conectada al sistema de
registro. Dado que se produjo antes de comenzar la adquisicion de datos, el episbdio no
25 fue captado por el EEG.
En dosis de 30 mg/kg, todas las ratas a las que se les administró la sal de
clorhidrato de bupropion pero no la sal de bromhidrato de bupropion mostraron estereotipos/hiperactividad.
En dosis de 60 mg/kg, todas las ratas a las que se les administrO la sal de
30 clorhidrato de bupropion.o la sal de bromhidrato de bupropion mostraron
estereotipos/hiperactividad. Una rata en el grupo de bromhidrato de bupropion tuvo un
clono fatal de todo el cuerpo inmediatamente despuØs de la administración antes de ser conectada al sistema de registro. Dado que se produjo antes de comenzar la adquisición
de datos, ci episodio no fue captado por el EEG.
35 En dosis de 100 mg/kg, todas las ratas a las que se les administró la sal de clorhidrato de bupropion o la sal de bromhidrato de bupropion mostraron estereotipos/hiperactividad. Las convulsiones expresadas por cualquiera de las formas de

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bupropion se manifestaron como clonos faciales con o sin incorporación adicional y
clorios de miembros anteriores. La diferencia en la cantidad de ratas con crisis

convulsivas fue estadIsticamente significativa (p 0,05) (Tabla 41).
Los resultados de este estudio muestran que el bromhidrato de bupropion tiene
5 una concentración mÆs baja para inducir convulsiones comparado con el clorhidrato de
bupropion. A diferencia del clorhidrato de bupropion, la forma sauna de bromhidrato de bupropion indujo menos convulsiones en menos animales. Las convulsiones de comportamiento fueron leves y estuvieron acompanadas por actividad de crisis
convulsivas elØctrica. Las actividades de crisis convulsivas breves observadas en los
10 hipocarnpos de 3 ratas son muy probablemente descubrimientos incidentales, ya que
ocurrieron de manera aparentemente aleatoria. Sin embargo, se observaron reacciones inmediatas inesperadas en una rata a la que se le administró una dosis de 10 mg/kg y en
una rata a la que se le administró una dosis de 60 mg/kg de bromhidrato de bupropion
I* que podria demandar mÆspruebas.
15
EJEMPLO 5: ACTIVIDAD CONVULSIVA DE SALES CLORHIDRATO Y
BROMHIDRATO DE BUPROPION
I.

Se realizaron dos estudios para investigar las propiedades proconvulsivas relativas de dos
20 sales de bupropion. En la primera instancia se realizó un estudio de telemetrIa para establecer el
intervalo de dosificación adecuado para el estudio principal. En cada estudio se dividió a los
ratones en dos grupos de dosis y se los inyectó intraperitonealmente con bupropion 14C1 o con bupropion HBr.
En el postratamiento los ratones fueron observados continuamente durante un perlodo de
120 minutos seguido de observaciones periOdicas a 135 minutos, 150 minutos, 165 minutos, 180 minutos, 210 minutos, 240 minutos, 300 minutos y 24 horas para incidencia e intensidad de convulsiones clónicas. La convulsion clónica fue definida como la rigidez del animal seguida de sacudidas, movimientos bruscos. Las convulsiones fueron clasificadas como leves, moderadas y graves de acuerdo con las siguientes descripciones.

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Leves: Cabeza y cola ligeramente extendidas y pocas sacudidas
Moderadas: Cabeza y cola totalmente extendidas y algunas sacudidas
Graves: Cabeza y cola totalmente extendidas con fuertes sacudidas

35 Estudio de telemetrIa

Se dividieron los ratones CD-1 en grupos de dosis (grupo N=3/dosis) y se los inyectó intraperitonealmente con las siguientes dosis de Bupropion HC1 75, 100, 125 o 150 mg/kg con

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una serie paralela de grupos de dosis administradas con un intervalo de dosificaciOn equimolar
de Bupropion HBr. Los descubrimientos registrados en el postratamiento inciuyeron una observación continua durante 120 minutos Para evidencia de convulsiones clónicas, y observaciones intermitentes (fijas) durante 24 horas para otros signos, inclUidos convulsiones tónicas, movimiento, actividad, parÆlisis, marcha y evidencia de recuperación.

Estudio principal
Se dividió a los ratones CD-i en grupos de dosis (grupo N10/dosis) y Se los inyectó intraperitonealmente con las siguientes dosis de Bupropion HC1 100, 125 o 150 mg/kg con una serie paralela de grupos de dosis administradas con un intervalo de dosificación equimolar de Bupropion HBr. En ci postratamiento los ratones fueron observados continuamente durante un perlodo de 120 minutos Para incidencia e intensidad de convulsiones clónicas.
Resultados
Estudio de telemetria

El Bupropion HBr tuvo, aparentemente, un umbral mÆs alto (125mg/kg) Para
convulsiones tónicas que el grupo de Bupropion HC1 (100 mg/kg) y una tendencia a recuperarse mÆs rÆpidamentede otros signos relacionados con el tratamiento. Se encontró que la incidencia y la intensidad de las convulsiones ciOnicas proporcionaron una base cuantal Para la comparación de los dos tratamientos, que se resumen en la siguiente Tabla.

Incidencia e intensidad de las convulsiones clónicas en ratones CD-i dosificados intraperitonealmente con Bupropion HC1 o Bupropion HBr (Estudio de telemetrIa, grupo N3/dosis).

Cantidad media de convulsiones/ratOn

Dosis (mg/kg) Bupropion HC1 Bupropion HBr
75 0 0

100 1,0 (2/3)* 0
125 6,0 (3/3)* 8,0 (3/3)*
150 32,0(3/3) 1i3O(3/3)*
El fivel de dosis se indica como Bupropion 1-Id, El Bupropion HBr se administra on niveles equimolares
* Los nümeros entre parntesis son cantidades de ratones que tuvieron convulsiones on cada grupo de dosis.

Estudio principal
En el postratamiento los ratones fueron observados continuamente durante un perlodo de 120 minutos Para incidencia de convulsiones clOnicas, como se muestra en la Tabla siguiente

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Incidencia e intensidad de las convulsiones clónicas en ratones CD-1 dosificados intraperitonealmente con Bupropion HC1 o Bupropion HBr (Segundo estudio, grupo N40/dosis).

Cantidad media de convulsiones/ratón

Dosis (mg/kg) Bupropion HC1 Bupropion HBr
100 0 1,0(3/10)*
125 16,0 (10/10)* 14,3 (8110)*
150 82,7 (10/10)* 57,3 (10/10)
El nivel de dosis se indica como Bupropion HCI, El Bupropion HBr se administra en niveles equimolares
* Los nümeros entre parØntesis son càntidades de ratones que tuvieron convulsiones en cada grupo de dosis.

Estudios combinados

Los datos agrupados para los dos estudios para la incidencia de convulsiones clónicas se muestran en la siguiente tabla:
Incidencia e intensidad de las convulsiones clónicas en ratones CD-1 dosificados intraperitonealmente con Bupropion HCI o Bupropion HBr (Datos agrupados, grupo N=13ldosis).

Cantidad media de convulsioues/ratón
Dosis (mg/kg)5 Bupropion HCL Bupropion HBr
100 0,2 (2/13)* 0,8 (3113)*
125 13,7(13113)* 12,8(11/13)*
150 71,0(13/13)* 46,6(13/13)*
El nivel de dosis Sc indica como Bupropion HCI. El Bupropion HBr se administra en niveles equimolares
* Los nümeros entre parØntesis son eantidades de ratones que tuvieron convulsiones en cada grupo de dosis.

La siguiente Tabla muestra los datos agrupados para gravedad de convulsiones clónicas. Intensidad de las convulsiones clónicas en ratones CD-1 dosificados intraperitonealmente con Bupropion HC1 o Bupropion HBr (Datos agrupados, grupo N=13ldosis).
Intensidad media de convulsiones/ratón del total

Dosis (mg/kg) Bupropion IIC1 Bupropion HBr

Graves 66,7 0,0
Moderadas 33,3 10,0

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Leves 0,0 90,0

125
Graves 71,9 47,3
Moderadas 10,1 31,7
Leves 18,0 21,0

150
Graves 79,0 53,0
Moderadas 12,2 25,7
Leves 8,8 21,3
El nivel de dosis se indica como I3upropion UCI. El Bupropion HBr se administra en niveles equimolares

Dc los resultados anteriores se desprende claramente que la dosis umbral para la
5 inducción de convulsiones clónicas para ambas sales es aproximadamente 100 mg/kg (como bupropion HC1). A este nivel, debido a la baja cantidad de convulsiones observadas por ratón, es dificil discernir diferencias significativas entre las dos formas salinas, aunque Si se observa una atenuación de la gravedad de las convulsiones con la sal HBr.
En el nivel de dosis de 125 mg/kg se observa una reducción de 6,6% en la cantidad media
10 de convulsiones por ratón y una reducción de 15,4% en la cantidad de ratones convulsivos. AdemÆs,parecerla queen este nivel la sal HC1 ha alcanzado el mÆximo desu curva de respuesta
de dosis mientras que este no es ci caso para la sal HBr. Como se observa en el nivel de dosis de
100 mg/kg, la gravedad de las convulsiones tambiØn se atenüa con una reducción de 34,2% en el
% de convulsiones graves observadas.
15 En el nivel de dosis de 150 mg/kg, ambas formas salinas se encuentran en el mÆximo de sus curvas de respuesta de dosis. Sin embargo, la reducción de la cantidad media de
convulsiones por ratón es aün mÆs marcada que en el nivel de dosis de 125 mg/kg con una
reducción de 34,4% en lit cantidad de convulsiones observadas. Nuevamente, la gravedad de las convulsiones se atenüa con una reducción de 32,9% en ci % de convulsiones graves observadas.

20
II.

Se realizó tambiØn un anÆlisisestadistico para investigar las propiedades
proconvulsivas relativas de las dos sales de bupropion: clorhidrato de bupropion y
bromhidrato de bupropion.

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En el postratamiento los ratones fueron observados continuamente durante un perlodo de
120 minutos para incidencia e intensidad de convulsiones clónicas. Se registraron la
cantidad y la intensidad de las convulsiones. A continuaciOn se presentan los datos.

Cantidad de convulsiones por ratón por gravedad (Datos agrupados grupo N=13/dosis).
Dosis (mg/kg) Intensidad de
las
convulsiones

Cantidad media de convulsiones/ratón (Cantidad
total)
Bupropion HC1 (N= 13) Bupropion FIBr
(N=13)
100 Grave 0,15(2) 0,0(0)
100 Moderada 0,08(1) 0,08(1)
100 Leve 0,0(0) 0,69(9)
125 Grave 9,85 (128) 6,08 (79)
125 Moderada 1,38 (18) 4,08 (53)
125 Leve 2,46 (32) 2,69 (35)
150 Grave 56,08(729) 24,69 (321)
150 Moderada 8,69 (113) 12,00 (156)
150 Leve 6,23 (81) 9,92 (129)
* El nivel de dosis se indica como Bupropion HC1. El Bupropion HBr se administra en niveles equimolares

Leve: Cabeza y cola ligeramente extendidas y pocas sacudidas;
Moderada: Cabeza y cola totalmente extendidas con algunas sacudidas;
Grave: Cabeza y cola totalmente extendidas con fuertes sacudidas. AnÆlisisestadIstico: Paso 1: Detectar diferencias generales en los patrones de ocurrencia de convulsion en tØrminos de intensidad entre las sales de clorhidrato de bupropion y bromhidrato de bupropion. Se realizó la prueba Cochran-Mantel-Haenszel, la que mostró que la asociación entre las sales (clorhidrato de bupropion o bromhidrato de bupropion) y la gravedad de las convulsiones, controlando para esos niveles, era estadisticamente significativa (p 0,0001). Los resultados indicaron que, con cualquier nivel de dosis, hubo evidencia estadIstica de que ambas sales tenlan patrones diferentes en tØrminos de intensidades de las convulsiones.
Paso 2: Investigar mÆsaun los patrones de ocurrencia de convulsion utilizando modelos de regresión de Poisson logarItmicos lineales. Se analizO la cantidad de convulsiones utilizando los modelos de regresiOn de Poisson logarItmicos lineales con formulación, dosis y gravedad como predictores. Con el modelo de efectos principales (el modelo sOlo con efectos principales de formulación, dosis y gravedad) se mostró que, ajustado para 267

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dosis y gravedad, las probabilidades de varias convulsiones del grupo de clorhidrato de bupropion vs.. el grupo de bromhidrato de bupropion es exp(0,3436)1,41, o un aumento
de 41%. Este aumento fue estadisticamente significativo (p 0,001). Otras investigaciones revelaron que hay un perlodo de interacción significativa entre formulación y gravedad (p 0,001). Mientras ci grupo clorhidrato de bupropion tuvo mÆsconvulsiones graves, el grupo bromhidrato de bupropion tuvo mÆsconvulsiones leves y moderadas. La cantidad relativa de convulsiones registrada se muestra en la FIG. 26.

AdemÆs, los datos tambiØnpueden presentarse como la tabla acumulativa. En todos los casos excepto uno (0,23 vs. 0,77, todos en 100 mg/kg), ci grupo clorhidrato de bupropion tuvo una incidencia acumulada mayor de convulsiones comparado con el grupo bromhidrato de bupropion. Esto se ye mÆs elaramenteen la dosis mÆs alta analizada (150 mg/kg)

Cantidad de convulsiones por ratón por gravedad - Acumulado (Datos agrupados grupo N13/dosis).
Dosis (mg/kg) Intensidad de
las
convulsiones

Cantidad media de convulsiones/ratOn
Bupropion HC1 (N=13) Bupropion HBr
(N=13)
100 Grave 0,15 0,0
100 Grave+
Moderada

0,23 0,08

100 Todas 0,23 0,77
125 Grave 9,85 6,08
125 Grave+
Moderada

11,23 10,16

125 Todas 13,69 12,85
150 Grave 56,08 24,69
150 Grave+
Moderada

64,77 36,69

150 Todas 71,00 46,61

* El nivel de dosis se indica como Bupropion HC1. El Bupropion HBr se administra en niveles equimolares

El estudio principal mostró que la mayor incidencia de convulsiones se observó en el grupo clorhidrato de bupropion comparado con el grupo bromhidrato de bupropion. El aumento fue, en promedio, de 41%, y fue estadisticamente significativo (p 0,001).

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Ademªs, el grupo clorhidrato de bupropion pareció tener muchas mªs convulsiones graves en proporciones coinparado con el grupo bromhidrato de bupropion.
En tØrminos de incidencia acumulativa, los datos en bruto mostraron tendencias muy
claras de que la sal clorhidrato de bupropion era consistentemente superior comparada
con la sal bromhidrato de bupropion.

EJEMPLO 6: Estudios de estabilidad y disolución comparativa
La estabilidad de Bupropion HBr en diversas condiciones y en ciertas realizaciones de la invenciOn the investigada y comparada con Bupropion HC1. AdemÆs seinvestigaron los
10 perfiles de disolución de los comprimidos de Bupropion HBr XL en diversos medios. Por
ejemplo, se midieron los perfiles de disolución de los comprimidos de Bupropion HBr
XL de 174 mg y 348 mg en los siguientes medios: HO 0,1 N, agua, solución
amortiguadora de acetato (pH 4,5), solución amortiguadora de fosfato (pH 6,2), 5%
etanol en HC1 0,1 N, 20% de etanol en HC1 0,1 N, y 40% de etanol en HC1 0,1 N.
15 AdemÆs,se midieron los perfiles de disolución de los comprimidos de Bupropion HBr
XL de 522 mg en los siguientes medios: HC1 0,1 N, 5% etanol en HC1 0,1 N, 20% etanol
en FTC! 0,1 N, y 40% etanol en FTC! 0,1 N.
En los siguientes estudios de estabilidad se hicieron pruebas de Bupropion HBr en
forma de comprimidos XL segün las pautas de ICH en condiciones de temperatura y
20 humedad constantes por perlodos de 0, 3, 6, 9 y 12 mesesa 25°C +1- 2°C y 60 +1- 5% de
humedad relativa (HR) y en condiciones aceleradas de 40°C +/- 2°C y 75 +1- 5% HR, lo
que permitió el cÆlculo/estimación de datos de estabilidad a 18 meses. Los comprimidos
de Bupropion HBr XL se almacenaron en envases a granel (bolsas de LDPE y tambores
de fibra) y en botellas de HDPE de 7, 30 y 90 unidades. Las muestras fueron expuestas a
 5 condiciones controladas de humedad y temperatura en una cÆmara de estabilidad.
Luego de la exposición, los comprimidos fueron ana!izadas para descripción fisica,
contenido de humedad mediante Karl Fischer, contenido e impurezas mediante HPLC y propiedades de disoluciOn despuØs de 3, 6, 9 y 12 meses. La prueba de disolución se
realizó mediante la coloeación de la muestra de prueba en 900 ml de HC1 0,1 N a 37°C
30 +/- 0,5°C en un Aparato de Disolución USP Tipo 1 automatizado (Cesta) con una
agitación de 75 rpm. Se analizaron las muestras y el activo estÆndar debromhidrato de bupropion con un espectrofotómetro de UV a una longitud de onda de 252 nm.
Los comprimidos de Bupropion HBr XL utilizados en los estudios de estabilidad y de disolución fueron preparados mediante la granulación de Bupropion HBr en un lecho
35 fluido utilizando una solución acuosa de alcohol polivinIlico utilizando teenologla
superior de pu!verización con una hoquilla de 0,8 mm. Luego de la granulaciOn y el secado, los grÆnulos se tamizan atravØs de un cedazo de 1,4 mm y se mezclan con

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lubricante behenato de glicerilo (por ejemplo, Compritol 888 ATO) en un mezclador para producir una mezela a granel. Luego se comprirne la mezela a granel en comprimidos utilizando una compresora de comprimidos Fette2200.
Los comprimidos se recubrieron en un revestidor de comprimidos con una solución de
5 recubrimiento preparada al mezclar una mezcla homogeneizada (homogeneizador
DeBee) de sebacato de dibutilo y polietilenglicol 4000 en alcohol etIlico 190-200 de graduación en el que se ha incorporado etilcelulosa y polivinilpirrolidona (por ejemplo, povidona) utilizando una unidad de dispersion de polvo, y recubierto eon cera carnauba.
Se realizaron experimentos de disolución in vitro en comprimidos de Bupropion HBr XL
10 de 174 mg, 348 mg y 522 mg utilizando aparatos Tipo 1 de la USP con una velocidad de
rotación de 75rpm, temperatura de 37°C – 0,5°C, 900m1 de medios de disolueiOn y deteceiOn de longitud de onda UV de 252mm Los medios de disoluciOn incluyeron HC1
0,1 N (100%); Etanol (5%) con HC1 0,1 N (95%); Etanol (20%) con HC1 0,1 N (80%); y Etanol (40%) con HCl 0,1 N (60%). Los experirnentos de disoluciOn investigaron los
15 riesgos de absorciOn rÆpidade la dosis inducida por alcohol en las fonnas farmacØutieas
anotadas. Se proporcionaron datos de la disoiución: despuØs de 2 horas para todas las
fonnas farmacØuticas para 12 comprimidos en HC1 0,1 N, 5% etanol en HC1 0,1 N, 20% etanol en HC1 0,1 N, y 40% etanol en HC1 0,1 N; despues de 16 horas para 6 de los comprimidos de Bupropion HBr XL de 522 mg en HC1 0,1 N, y 40% etanol en HC1 0,1
20 N; y despuØs de 20 horas para 6 de los comprimidos de Bupropion HBr XL de 174 mg y
348 mg en HC1 0,1 N, y 40% etanol en HC1 0,1 N. En todos los casos, los perfiles de
disolución mostraron que el perfil de velocidad de liberación del producto farmacØutieo
de Bupropion HBr fue mÆs lento enpresencia de alcohol (por ejemplo, 40% etanol)
comparado con el perfil de velocidad de liberaciOn de la misma fornia farmacØutica en
025 100% }-ICl 0,1 N.

Los resultados se muestran abajo y en las Figuras 27-32, donde el Compuesto C
es el producto de degradación de bupropion intermedio 20U78, el Compuesto B es el
producto de degradacion de bupropion intermedio 827U76, y el Compuesto F es el
30 producto de degradaciOn de bupropion intermedio 852U77:

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Bupropion HBr 174 mg/348 mg - EvaluaciOn de datos de estabilidad
Condición: 25°C / 60% HR;
Tiempos de muestreo: 0, 3, 6, 9, 12 meses

174 mg
Articulo de prueba % Cambio I mes Total de cambios (%) eu 18

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meses (segün cÆlculo)
DisoluciOn
2horas +0,17% +3,1%
4horas +0,13% +2,3%
8 horas -0,09% -1,6%
16 horas
Ensayo
Acido 3-clorobenzoico +0,003% +0,05%
Compuesto C +0,0008% +0,01%
Compuesto E
Compuesto F +0,003% +0,05%
Total de impurezas +0,007% +0,13%

348 mg
ArtIculo de prueba Cambio I mes Total de cambios (%) en 18
meses (segun cÆlculo)
Disolución
2horas +0,12% +2,2%
4 horas
8 horas --
16 horas +0,06% +1,1%
Ensayo
Acido 3-clorobenzoico +0,003% +0,05%
Compuesto C +0,001% +0,02%
Compuesto B
Compuesto F +0,003% +0,05%
Total de impurezas +0,007% +0,13%

Comparación de datos de estabilidad - Bupropion HCJ vs.. Bupropion HBr
Los comprimidos de Bupropion HBr (dosificaciones de 174, 348 & 522 mg) fueron en forma de comprimidos XL como se describe anteriormente. Los comprimidos de Bupropion HC1 (dosificaciones de 150 & 300 mg) se realizaron de La misma manera que los comprimidos de Bupropion HBr. Los comprimidos de Bupropion HC1 tuvieron la misma formulaeión que los comprimidos de Bupropion HBr con la excepción de que los comprimidos de Bupropion HCl tuvieron un recubrimiento de barrera contra la humedad que rodeaba el recubrimiento de liberaciOn controlado, y un plastificante diferente en los
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recubrimientos. Los ingredientes del 2° recubrimiento (esto es, el recubrimiento de
barrera contra la humedad) en los comprimidos de Bupropion HC1 fueron: Eudragit L30D
55 (polimero formador de pelIcula, 2,4% total en comprimido de 150 mg; 1,9% total en comprimido de 300 mg) PEG 1450 (0,3% en 150 mg, 0,25% en 300 mg), dióxido de silicio (0,9% en 150 mg; 0,7% en 300 mg), citrato de trietilo (0,12% en 150 mg; 0,097% en 300 mg). El plastificante utilizado en los recubrimientos de los comprimidos de Bupropion HC1 fue PEG1450 en las siguientes cantidades: Comprimido de Bupropion HC1 de 150 mg: PEG1450=1,8% total (1,5% en ler recubrimiento; 0,3% en 2° recubrimiento); Comprimido de Bupropion HC1 de 300 mg: PEG14501,2% total (0,95% en 1 er recubrimiento; 0,25% en 2° recubrimiento). El recubrimiento de liberaciOn controlada del comprimido de Bupropion HBr tuvo un plastificante mezcla de sebacato de dibutilo y PEG4000.

Limites de especificación experimental
Comparación de resultados a 12 meses (25°C 60% HR)
Contenido: 90% 110% de LC
Acido 3-clorobenzoico NMA 0,7%
Compuesto relacionado C NMA 0,3%
Compuesto relacionado E NMA 0,4%
Compuesto relacionado F NMA 1,0%
Total de impurezas NMA 2,5%

Comparacion de datos de estabthdad a 12 meses
(25°C 60% HR)

Prueba

Bupropion IIC1 Bupropion HBr

150 mg 300 mg 174 mg 348 mg
Contenido 94,7% 97,5% 98,3% 97,9% Acido 3-
clorobenzoico

0,14% 0,13% 0,04% 0,04%

Compuesto C 0,00% 0,01% 0,04% 0,03%

CompuestoE 0,01% 0,01% 0,01% 0,01%

Compuesto F 0,12% 0,09% 0,05% 0,05%

Total de impurezas 0,38% 0,35% 0,21% 0,21%
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Disolución

2horas 2,3% 352% 32,5% 33,7%
4 horas 24,8% 26,6% 61,8% 59,2%
8 horas 72,5% 67,0% 95,6% 90,4%
16 horas 95,5% 94,1% 99,8% 98,6%

Limites de especificaciOn experimental
Comparación de resnitados a 18 meses profØticos (25°C I 60% HR)
Contenido: 90% 110% de LC
Acido 3-clorobenzoico NMA 0,7%
Compuesto relacionado C NMA 0,3%
Compuesto relacionado E NMA 0,4%
Compuesto relacionado F NMA 1,0%
Total de impurezas NMA 2,5%

Comparación de datos de estabilidad profØtica segæn cÆlculO a 18meses
(25°C 60% HR)

Prueba

Bupropion HC1 (Prueba real) Bupropion HBr

(Resultados pronosticados)
150 mg 300 mg 174 mg 348 mg
Contenido 95,7% 98,0% 97,3% 97,9% Acido 3-
clorobenzoico

0,18% 0,16% 0,06% 0,06%

Compuesto C 0,01% 0,02% 0,04% 0,04%

Compuesto E 0,01% 0,02% 0,01% 0,01%

Compuesto F 0,12% 0,11% 0,06% 0,06%
Total de impurezas 0,41% 0,36% 0,26% 0,26%
DisoluciOn
2horas 2,5% 3,4% 33,4% 34,6%
4 horas 26,6% 27,1% 62,2% 59,0%
8horas 72,1% 65,5% 94,9% 91,0%
16 horas 95,4% 93,4% 100,3% 98,6%

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Limites de especificación experimental
Comparación de resultados a 6 meses (25°C I 60% HR)
Contenido: 90% 110% de LC
Acido 3-clorobenzoico NMA 0,7%
Compuesto relacionado C NMA 0,3%
Compuesto relacionado E NMA 0,4%
Compuesto relacionado F NMA 1,0%
Total de impurezas NMA 2,5%

Comparacion de datos de estabihdad a 6 meses
(25°C 60% HR)

Prueba

Bupropion HC1 Bupropion HBr

150 mg 300 mg 174 mg 348 mg 522 mg
Contenido 96,6 98,3 98,03 97,21 98,08
Acido 3- 0,10 0,09 0,03 0,03 0,03
Compuesto 0,02 0,02 0,02 0,02 0,04 Compuesto 0,02 0,01 0,01 0,01 0,01 Compuesto 0,12 0,10 0,05 0,05 0,04
Total de impurezas 0,35 0,33 0,16 0,17 0,18
Disolución
2 horas 2,40 3,50 32,28 33,87 32,26
4horas 25,79 28,77 61,96 59,96 55,30
8horas 73,88 69,47 95,87 91,72 85,09
16 horas 96,02 94,60 99,93 98,44 98,96

TambiØn se obtuvieron datos de disoluciOn para comprimidos de Bupropion HC1 como se muestra arriba (150 mg y 300 mg) pero teniendo los comprirnidos de Bupropion HCl solo un recubrimiento de liberación controlada (esto es, sin el recubrimiento de barrera contra la humedad) del modo siguiente:
1 hora: 28-32%
2 horas: 50-55%
3 horas: 70-75%
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4 horas: 85%
5 horas: aproximadamente 100%
en HC1 0,1 N utilizando un Aparato I de la USP a 75 rpm y 37– 0,5CC.

EJEMPLO 7: Estudios de biodisponibilidad/farmacocinØticos (PK)

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Estudio de biodisponibilidad comparativa, en ayunas, con varias dosis, abierto, con doble intercambio de tratamiento de comprimidos de Bupropion HBr XL de 348 mg versus Comprimidos Weilbutrin XLfi de 300 mg en sujetos masculinos y femeninos normales,
10 saludables, no fumadores. Estudio B06-756PK-10121 (3230)

En este estudio se estudió la velocidad y ci aicance de absorción de comprimidos de Bupropion HBr XL de 348 mg relativos a comprimidos Weilbutrin XLfi de 300 mg en condiciones de ayuno con varias dosis. El estudio mostró que los comprimidos de
15 Bupropion HBr XL de 348 mg eran equivalentes a los comprimidos Welibutrin XLfi de
300 mg en condiciones de ayuno con varias dosis.

Los resultados se muestran abajo y en las Figuras 33-37.

20 Diseflo de estudio y fase de desarrollo:
Estudio de biodisponibilidad relativa, en ayunas, con varias dosis, abierto, en estado estacionario, aleatorio, con doble intercambio de tratamiento.

Objetivos:
El objetivo de este estudio fue comparar la velocidad y el alcance de absorción de
bupropion de una formulación nueva de comprimidos de Bupropion HBr XL de 348 mg versus los comprimidos Welibutrin XLfi de 300 mg de referencia en un estado
estacionario (SS) en condiciones de ayuno.

30 Criterios principales a incluir:
Sujetos masculinos y femeninos normales, saludables, no fumadores en edades entre 18 y

55 aæos.

Producto con dosificaeión, nümero de lote y via de administración:
35 Luego de una noche de ayuno de al menos 10 horas, 1 comprimido Welibutrin XLfi de
150 mg, lote #: 05K077P, administrado por via oral con 240 mL de agua a temperatura ambiente en los dias 1 a 3 de cada periodo de estudio.

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Producto de pruebalproducto en investigación, nümero de lote y via de administraciOn: Luego de una noche de ayuno de al menos 10 horas, 1 comprimido de Bupropion HBr
XL de 348 mg, lote #: 06C159P (valor de concentración= 97,0% de afirmaciones de
5 etiquetado), administrado por via oral con 240 mL de agua a temperatura ambiente en los
dIas 4 a 13 de cada perlodo de estudio.

Producto de referencia, nümero de lote y via de administración:
Luego de una noche de ayuno de a! menos 10 horas, 1 comprimido Welibutrin XLfi de
10 300 mg, lote #: 06C090P (valor de concentración= 99,3% de afirmaciones de etiquetado),
administrado por via oral con 240 mL de agua a temperatura ambiente en los dIas 4 a 13
de cada perlodo de estudio.

Cantidad de sujetos (planificados y analizados):
15 En el Perlodo I hubo 48 sujetos dosificados, de los cuales 40 completaron el estudio. Los
anÆlisis farmacocinØticosy estadIsticos finales se realizaron en 38 de los 40 sujetos que completaron el estudio.

Tiempos de muestreo de extracción sanguinea:
20 Durante cada perIodo de estudio se recogieron 19 muestras de sangre de cada sujeto en
los siguientes tiempos de muestreo:
Dias 1, 10, 11, y 12: 0,00 hora (dosis previa)
Dia 13: 0,00 (dosis previa), 1,00, 2,00, 3,00, 4,00, 5,00, 6,00, 7,00, 8,00, 10,00, 12,00,
14,00, 16,00, 20,00, y 24,00 horas dosis posterior.
25 No se tomaron muestras de sangre en los dIas 2, 3, 4, 5, 6, 7, 8, y 9.
Todas las muestras de sangre de dosis previas se tomaron dentro de los 10 minutos
previos a la dosificaciOn.

Procedimiento bioanalItico:

30 El bupropion y sus metabolitos, eritroamino alcohol de bupropion, treoamino alcohol de
bupropion, hidroxibupropion, y el estÆndarinterno, 1 -(3-clorofenil)-piperazina, se extrajeron mediante extracción de fase sólida en un medio orgÆnico de0,50 mL de
plasma humano. Se inyectó una alIcuota de este extracto en un sistema cromatografico liquido de alto rendimiento y se detectO utilizando un espectrómetro de masa en tandem.
35 Se separaron los analitos mediante cromatografia de fase reversa. La evaluaciOn del
contenido se llevó a cabo mediante la construcciOn de una curva de calibración de 8
puntos (con exclusion de concentraeión cero) que cubre el rango de 1,000 ng/mL a

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1023,900 ng/mL para bupropion, 1,000 ng/mL a 1023,900 ng/mL para eritroamino
alcohol de bupropion, 1,000 ng/mL a 1023,900 ng/mL para treoamino alcohol de
bupropion y 3,906 ng/mL a 3999,600 ng/mL para hidroxibupropion en plasma humano.
La pendiente y la interceptación de las curvas de calibración se determinaron mediante anÆlisisde regresión lineal pesado (1/area pico2). Se analizaron dos curvas de calibración y muestras QC por duplicado (en tres niveles de concentración) junto con cada lote de las muestras de estudio. Las relaciones de area pico se utilizaron para determinar la concentraeión de los estÆndares, las muestras de control de calidad y las muestras de estudio desconocidas de las curvas de calibración.

Criterios para la evaluación:
El anÆlisis farmacocinØtico se realizó en 38 sujetos que cornpletaron los 2 perIodos de estudio. La evaluación de seguridad se realizó en todos los sujetos que recibieron al
menos 1 dosis durante el transcurso del estudio.
15

FarmacocinØtica (PK):
Se calcularon los siguientes parÆmetros farmacocinØticos para bupropiony sus
metabolitos hidroxibupropion, treoamino alcohol de bupropion y eritroamino alcohol de bupropion, mediante mØtodos estÆndar no compartimentales: AUC,CmÆx, CmIn, Cprom,
20 MRT, relación MR. % de fluctuación, % de oscilación y TmÆx. Estos parÆmetros
tambiØn se computaron para compuestos ponderados con actividad farmacologica
(PAWC).

MØtodos estadIsticos:

025 Mediante el uso de los procedimientos del Modelo Lineal General (GLM) en el Sistema
de AnÆlisisEstadIstico (SAS) se realizó el anÆlisis de variancia (ANOVA) en AUC, CmÆx,Cmin, Cprom In transformados y en MRT, relaciOn MR, % de fluctuación, % de osciiación y TmÆx no transformadosen un nivel significativo de 0,05. Se calculó el
coeficiente de variación (CV) intrasujeto mediante ci Error CuadrÆtico Medio (MSE) de
30 la tabla de ANOVA. La relación de medias geomØtricas y el intervalo de confianza
geomØtrica de 90% (C.I. de 90%) se ealcularon sobre la base de la diferencia on los
Medios de Minimos Cuadrados de los AUC, CmÆx, CmIn In transform.ados, entre la
prueba y formulaciones de referencia. La TmÆx se analizó utilizando mØtodos no paramØtricos.
35
PARAMETROS FARMACOCINETICOS PARA BUPROPION:

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ParÆmetros Media geoniØtrica (%CV)
farmacocinØticos Media aritmØtica SD
Comprimidos de Bupropion Comprimidos Weilbutrin XLfi
HBr XL de 348 mg (A) de 300 mg (B) (n38)
(n=38)
AUCt (ng1ir/mL) 1362,44 (24,53) 1541,27 (20,43)
1409,24 345,72 1575,03 321,80
Cmªx (ng/mL) (28,44) 151,03 (27,15)
134,33 38,20 156,83 42,57
Cmin (ng/mL) 24,72 (37,50) 26,95 (31,48)
26,60 9,98 28,32 8,92
Cprom (ng/mL) 56,77 (24,53) 64,22 (20,43)
58,72 14,41 65,63 13,41
TmÆx(hr) 4,01 (2,00 7,00) 4,50 (3,00 7,00)
Grado de fluctuación 187,51:17 53,50 195,47 147,80
(%)
Urado de oscilaciOn 475,44 280,21 499,74 228,53
(%)
MRT(hr) 9,12*0,72 9,76–0,69
medio (mm - max)

EVALIJACIONES DE BIODISPONIBILIDAD RELATIVA PARA BUPROPION;
ParÆmetro Datos no corregidos de concentración
C.I. de 90% Relación de medias CV intrasujeto
AUCt 84,19%a93,95% 88,93% 14,16%
CmÆx 80,20% a 92,15% 85,97% 17,97%
Cmfn 86,56% a 100,00% 93,04% 18,68%
ParÆmetro Datos corregidos de concentraciOn
C.I. de 90% Relación de medias
AUCO-t 86,18% a 96,18% 91,04%
AUCO-inf 82,10% a 94,33% 88,00%
CmÆx 88,61% a 102,37% 95,24%

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PARAMETROS FARMACOCINETICOS PARA HIDROXIBUPROPION:

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ParÆmetros Media geomØtrica (%CV)
farmacocinØticos Media aritmØtica SD

Comprimidos de Bupropion Comprimidos Weilbutrin XLfi
HBr XL de 348 mg (A) de 300 mg (B) (n38)
(n=38)
AUCt (nghr/mL) 218 15,79 (29,60) 25099,08 (29,19)
22879,88 6771,48 26180,58 7642,05
CmÆx(ng/mL) 1158,54 (28,08) 1344,33 (29,42)
1208,14 339,24 1403,10 412,83
CmIn(ng/mL) 762,55 (34,99) 895,28 (32,81)
814,63 285,05 944,00 309,69
Cprom (ng/mL) 908,99 (26,0) 1045,80 (29,19)
953,33 282,14 1090,86 318,42
TmÆx(hr) 6,00 (3,00 10,00) 7,00 (4,00 10,02)
Grado de fluctuación 43,46 16,88 43,12 17,82

Grado de oscilación 53,97 25,74 52,19 26,83

MRT(hr) 11,32–0,31 11,5110,29
RelaciónM/P 15,57–4,20 15,97–4,84
medio (min - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA HIDROXIBUPROPION:

Parªmetro Datos no corregidos de concentración
C.I. de 90% Relación de medias CV intrasujeto
AUCt 82,96% a 92,04% 87,39% 13,39%
Cmªx 81,93% a 91,10% 86,39% 13,68%
CmIn 81,45% a 90,94% 86,06% 14,22%

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PARAMETROS FARMACOCINETICOS PARA TREOAMINO ALCOHOL DE BUPROPION:

ParÆmetros Media geomØtrica (%CV)
farmacocinØticos Media aritmØtica SD
Comprimidos de Bupropion Comprimidos Weilbutrin XLfi
HBr XL de 348 tug (A) de 300 mg (B) (n=38)
(n38)
AUCt (nghr/mL) 8842,06 (37,35) 9768,54 (27,53)
9446,28 3528,05 10112,95 2783,98
CmÆx(ng/mL) 486,58 (34,68) 541,95 (26,73)
514,82+ 178,53 560,74– 149,88
Cmmn (ng/mL) 282,78 (47,91) 318,60 (34,19)
312,46 1149,70 335,65 114,75
Cprom (ng/mL) 368,42 (37,35) 407,02 (27,53)
393,60– 147,00 421,37– 116,00
TmÆx(hr) 6,00 (3,00 10,00) 7,00 (5,00 -14,00)
Grado de fluctuación 55,17 18,45 55,08 19,06
(%)
Grado de oscilación 74,98 32,28 72,78 31,30
(%)
MRT(hr) 11,39–0,37 11,60–0,28
Relación MIP 6,76 2,29 6,60 2,34
medio (min max)

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EVALUACIONES DE BIODISPONIBILIDAD RELATIVA DRA TREOAMINO \\J

ALCOHOL DE BUPROPION:

Pathmetro Datos no corregidos de concentración
C.I. de 90% Relaeión de medias CV intrasujeto
AUCt 85,78% a 96,23% 90,86% 14,83%
CmÆx 84,49% a 95,91% 90,02% 16,38%
CmIn 83,54% a 95,43% 89,29% 17,21%

PARAMETROS FARMACOCINETICOS PARA ERITROAMINO ALCOHOL DE BUPROPION:

ParÆmetros Media geomØtrica (%CV)
farrnacocinØticos Media aritmØtica SD

Comprimidos de Bupropion Comprimidos Weilbutrin XLfi
HBr XL de 348 mg (A) de 300 mg (B) (n=38)
(n=38)
AUCt (ngthr/mL) 1922,76 (29,01) 2091,51 (22,07)
2009,09+582,74 2143,79–473,12
CmÆx(ng/mL) 99,98 (27,31) 108,26 (23,57)
103,93–28,38 111,35–26,25
Cmin (ng/mL) 67,46 (35,71) 76,01 (25,97)
72,00–25,71 78,52–20,39
Cprom (ng/mL) 80,11 (29,01) 87,15 (22,07)
83,71 24,28 89,32 19,71
TmÆx(hr) 7,00 (5,00 14,00) 7,00 (5,00 12,00)
Grado de fluctuación 40,46 W 16,49 37,10 14,22
(%)
Grado de oscilación 50,16 24,94 43,65 19,18
(%)
MRT(hr) 11,54–0,32 11,72–0,25
RelaciOn M/P 1,47 0,45 1,40 0,42
medio (min - max)

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EVALUACIONES DE B1ODISPON1BILIDAD RELATIVA PARA ERITROAMINO ALCOHOL DE BUPROPION:

ParÆmetro Datos no corregidos de concentraciOn
C.I. de 90% RelaciOn de medias CV intrasujeto
AUCt 87,32% a 97,69% 92,36% 14,48%
Cmªx 87,66% a 97,91% 92,64% 14,27%
Cmin 83,81% a 95,28% 89,36% 16,57%

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PARAMETROS FARMACOCrNETICOS PARA BUPROPION TOTAL (PAWC):

ParÆmetros Media geomØtrica (%CV)
farruacocinØticos Media aritmØtica SD
Comprimidos de Bupropion Comprimidos Welibutrin XLfi
HBr XL de 348 mg (A) de 300 mg (B) (n=38)
(n=38)
AUCt (jiM.hr) 66,48 (26,44) 75,89 (24,59)
69,03 18,25 78,13 19,21
CmÆx(iM) 3,70 (24,37) 4,26 (25,37)
3,81 0,93 4,39– 1,11
CmIn (.iM) 2,21 (32,88) 2,57 (29,67)
2,34+-0,77 2,68 0,79
Cprom (.tM) 2,77 (26,44) 3,16 (24,59)
2,88–0,76 3,26–0,80
TmÆx(hr) 5,00 (2,00 10,00) 6,00 (4,00 10,02)
Urado de fluctuación 53,54 17,61 53,73 18,91
(%)
Grado de oscilación 69,50 29,41 68,34 30,09
(%)
MRT(hr) 11,15–0,32 11,38–0,31
medio (mfn -max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA BUPROPION TOTAL (PAWC):
ParÆmetro Datos no corregidos de concentración
C.I. de 90% Relación de medias CV intrasujeto
AUCt 83,72% a 92,62% 88,06% 13,02%
CmÆx 82,39% a 92,05% 87,09% 14,31%
Cmlii 82,48% a 91,87% 87,05% 13,91%

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ConclusiOn:

Se evaluaron los farmacocinOticos del bupropion luego de varias dosis orales de Comprimidos de Bupropion HBr XL de 348 mg (Tratainiento A) y Comprimidos
Welibutrin XLfi de 300 irig (Tratarniento B) en condiciones de ayuno,

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Se evaluaron los datos de biodisponibilidad coniparativa del bupropion, sus metabolitos y
los compuestos ponderados con actividad farmaeológica (PAWC) mediante la medición y coxnparación de la exposición pico y sistØrnica total de los dos tratamientos en estado

estacionario.
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Los resultados estadisticos indicaron que el estado estacionario se alcanzO el dia 13. Las relaciones de medios geomØtricos de pruebalreferencia y los correspondientes intervalos
. de confianza de 90% para AUCt, CmÆxy Crain estuvieron dentro del rango de 80,00%-
125,00% para bupropion, sus metabolitos y los PAWC en condiciones de ayuno en
15 estado estacionario. No hubo una diferencia significativa en los valores de TmÆxde
bupropion entre los dos tratamientos (valor p 0,05).

En conclusiOn, los comprimidos de Bupropion HBr XL de 348 mg demostraron una concentración pico equivalente, concentraciOn minima y exposición sistdmica relativa a
20 los comprimidos de Welibutrin XLfi de 300 mg en condiciones de ayuno en estado
estacionario.

En general, los comprimidos de Bupropion HBr XL de 348 mg fueron bien tolerados

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cuando se administraron en varias dosis en condiciones de ayuno y no surgieron
problemas de seguridad significativos.

Este estudio se reaiizO de conformidad con la GCP.

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Tabla: Parªmetros farmacocinØticos medios (+SD) para Bupropion (n = 38)

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Comprimidos de Comprimidos de
Bupropion HBr XL W de 300 mg
de 348 mg (06C090P)
(06C159) (n--3 8)
(n=38)
AUC0T(ng*hr/mL) 1409+ 346 1575+322
Cmªx(ng/mL) 134+38 156,8143
Cmin(ng/mL) 26,6–10,0 28,3–8,9
Cprom(ng/mL) 58,7+14,4 65,6+13,4
TmÆx(hr) 4,0 (2,0 7,0) 4,5 (3,0 7,0)
Grado de fluctuación 187,5:1: 53,5 195,5 1 47,8
(%)
Medio (rarigo)

Tabla: Resumen de estadisticas para Bupropion (n = 38)

Comprimidos de Bupropion HBr XL de 348 mg
Versus Comprimidos de Welibutrinfi XL de 300 mg

Relación de medias
geometricas

FIntervalo de confianza
geomØtrica de 90%
AUCO-t 88,93% 84,19 a 93,95%
CmÆx 85,97% 80,20a92,15%
Cmlii 93,04% 86,56 a 100,00%

Tabla: ParÆmetrosfarmacocindticos medios (+-SD) para Hidroxibupropion (n = 38)
Comprimidos de Comprimidos de
Bupropion HBr XL Welibutrin XLfi de
de348mg 300 mg
(06C159) (06C090P)
(n38) (n=38)
AUCO-’c (ng hr/mL) 22890+ 6771 26181– 7642
CmÆx(ng/mL) 1208,1 + 339,2 1403,1 + 412,8
Cmln (ng/mL) 814,6 285,1 944,0 309,7
Cprom (ng/mL) 953,3 282,1 1090,9 318,4

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Tmax (hr) 6,0 (3,0 10,0) 7,0 (4,0 10,0)
Grado de fluctuación 43,5 16,9 43,1 17,8
(%)
RelaciOn metabolito/ 15,6-+4,2 16,0 4,8
original
Medio (rango)

Tabla: Resumen de estadIsticas para Hidroxibupropion (n = 38)

Comprimidos de Bupropion HBr XL de 348 mg
Versus Comprimidos de Welibutrinfi XL de 300 mg

RelaciOn de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 87,39% 82,96 a 92,04%
CmÆx 86,39% 81,93a91,10%
Cmiii 86,06% 81,45 a 90,94%

5 Tabla: ParÆmetrosfarmacocinØticos medios (–SD) para treoamino alcohol de bupropion (n=38)
Comprimidos de Comprimidos de
de 348 mg Welibutrin XLfi de
(06C159) 300 mg
(n=38) (06C090P)
(n=38)
AUCO-t (ng hr/mL) 9446– 3528 10113 –2784
CmÆx(ng/nnL) 514,8 – 178,5 560,7 – 149,9
CmIn(ng/mL) 312,5– 149,7 335,7– 114,8
Cprom(ng/mL) 393,6– 147,0 421,4– 116,0
TmÆx(hr) 6,0 (3,0 - 10,0) 7,0 (5,0 - 14,0)
Grado de fluctuación 55,2– 18,5 55,1 19,1
(%)
Relaciónmetabolito/ 6,8–2,3 6,6–2,3
original
Medio (rango)

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Tabla: Resumen de estadIsticas para treoamino alcohol de bupropion (n = 38)

Comprimidos de Bupropion HBr XL de 348 mg
Versus Comprimidos de Weilbutrinfi XL de 300 mg

Relación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-T 90:86% 85,78 a 96,23%
CmÆx 90,02% 84,49 a 95,91%
Cmin 89,29% 83,54 a 95,43%

Tabla: ParÆmetrosfarmacocinØticos medios (–SD) para eritroamino alcohol de bupropion (n=38)
Comprimidos de Comprimidos de
de 348 mg Weilbutrinfi XL de
(06C159) 300 mg
(n=38) (06C090P)
(n=38)
AUC0-r(nghr/mL) 2009+583 2144+473
Cmax(ng/mL) 103,9–28,4 111,4–26,3
Cmin(ng/mL) 72,0–25,7 78,5–20,4
Cprom (ng/mL) 83,7 24,3 89,3 119,7
TmÆx (hr) 7,0 (5,0 14,0) 7,0 (5,0 12,0)
Grado de fluctuación 40,5:L 16,5 37,1 14,2

Relación metabolito/ 1,5 0,5 1,4 0,4
original
Medio (rango)

Tabla: Resumen de estadIsticas para eritroamino alcohol de bupropion (n = 38)

Comprimidos de Bupropion HBr XL de 348 mg
Versus Comprimidos de Wellbutrinfi XL de 300 mg

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Relación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-’r 92,36% 87,32 a 97,69%
CmÆx 92,64% 87,66 a 97,91%
Cmlii 89,36% 83,81 a 95,28%

Tabla: ParÆmetrosfarmacocinØticos medios (–SD) para PAWC (n 38)

ParÆmetros
farmacocinØticos

Comprimidos de
de 348 mg
(06C159)
(n=38)

Comprimidos de
Wde 300 mg
(06C090P)
(n38)
AUC0-t (rM hr) 69,0::L 18,3 78,1 + 19,2
CmÆx(M) 3,8–0,9 4,4–1,1
Cmln(iM) 2,3–0,8 2,7+0,8
Cprom(iM) 2,9–0,8 3,3–0,8
TmÆx(hr) 5,0 (2,0 10,0) 6,0 (4,0 10,0)

Grado de fluctuación
(%)

53,5 17,6 53,7 + 18,9

Medio (rango)

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Tabla: Resumen de estadisticas para PAWC (n = 38)

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Comprimidos de Bupropion HBr XL de 348 mg
Versus Comprimidos de Weilbutrinfi XL de 300 mg

Relación de medias
geomØtricas

Intervalo de confiaiza
geomØtrica de 90%
AUCO-t 88,06% 83,72% a 92,62%
CmØ.x 87,09% 82,39% a 92,05%
CmIn 87,05% 82,48% a 91,87%

Estudio de proporcionalidad de concentración de la dosis, en ayunas, con una itniea dosis, abierto, con doble intercambio de tratainiento de dos concentraciones de comprimidos de Bupropion HBr XL (2 x 174 mg versus 1 x 348 mg) en sujetos masculinos y femeninos normales, saludables, no fumadores. Estudio B06-755PK-10121 (3228)

En este estudio se evaluó la proporcionalidad de concentración de la dosis entre las concentraciones de 174 mg y 348 mg de comprimidos de Bupropion HBr XL en condiciones de ayuno eon dosis iinicas. Los comprimidos de Bupropion HBr XL de 174 mg, cuando se suministraron en 2 x 174 mg fueron equivalentes a los comprimidos de Bupropion HBr XL de 348 mg suministrados en 1 x 348 mg.

Los resultados se muestran abajo y en las Figuras 38-43.

Diseflo de estudio y fase de desarrollo:
Estudio de proporcionalidad de concentración de la dosis, en ayunas, con una ünica dosis, abierto, aleatorio, con doble intercambio de tratamiento.

Criterios principales a incluir:
Suj etos masculinos y ferneninos normales, saludables, no fumadores en edades entre 18 y
55 afios.

Tratamiento A: Producto de prueba/produeto en investigación, nimero de lote y via de
25 administración:

Luego de una noche de ayuno de a! menos 10 horas, 2 comprimidos de Bupropion HBr
XL de 174 mg, lote #: 06D029P (valor de concentraciOn 97,1% de afirmaciones de etiquetado), administrado por via oral con 240 mL de agua a temperatura ambiente.
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Tratamiento B: Producto de prueba, nümero de lote y via de administración:
Luego de una noche de ayuno de al menos 10 horas, 1 comprimido de Bupropion HBr
XL de 348 mg, lote #: 06C159P (valor de concentración = 97,0% de afinnaciones de
5 etiquetado), administrado por via oral con 240 mL de agua a temperatura ambiente.

Cantidad de sujetos (planificados y analizados):
En el Periodo I hubo 48 sujetos dosificados, de los cuales 46 completaron el estudio. Los anªlisis farmacocinØticos y estadisticos se realizaron en 46 sujetos que completaron el

10 estudio.

Tiempos de muestreo de extracción sanguInea:
Durante cada periodo de estudio se recogieron 22 muestras de sangre de cada sujeto en
los siguientes tiempos de muestreo: 0,00 (dosis previa), 1,00, 2,00, 3,00, 4,00, 5,00, 6,00,
15 7,00, 8,00, 10,00, 12,00, 14,00, 16,00, 20,00, 24,00, 36,00, 48,00, 60,00, 72,00, 120,00,
168,00, y 216,00 horas dosis posterior.

Procedimiento bioanalItico:

El bupropion, eritroamino alcohol de bupropion, treoamino alcohol de bupropion,
20 hidroxibupropion, y el estÆndarinterno, 1-(3-clorofenil)-piperazina, se extrajeron
mediante extracción de fase sólida en un medio organico de 0,50 ml, de plasma humano.
Se inyectó una allcuota de este extracto en un sistema cromatogräfico lIquido de alto rendimiento y se detectó utilizando un espectrómetro de masa en tandem. Se separaron
los analitos mediante cromatografia de fase reversa. La evaluación del contenido se llevó
025 a cabo mediante la construcción de una curva de calibraciOn de ocho (8) puntos (con
exclusiOn de concentración cero) que cubre el rango de 1,000 ng/mL a 1023,900 ng/mL
(en plasma humano) para bupropion, 1,000 ng/mL a 1023,900 ng/mL (en plasma
humano) para eritroamino alcohol de bupropion, 1,000 ng/mL a 1023,900 ng/mL (en
plasma humano) para treoamino alcohol de bupropion y 3,906 ng/mL a 3999,600 ng/mL
30 (en plasma humano) para hidroxibupropion. La pendiente y la interceptación de las
curvas de calibración se determinaron mediante anªlisis de regresiOn lineal pesado (1/area pico2). Se analizaron dos curvas de calibración y muestras QC por duplicado (en
tres niveles de concentraciOn) junto con cada lote de las muestras de estudio. Las
relaciones de area pico se utilizaron para determinar la concentración de los estÆndares,
35 las muestras de control de calidad y las muestras de estudio desconocjdas de las curvas de
calibración.

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Criterios para la evaluación:

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El anÆlisisfarmacocinØtico se realizó en 46 sujetos que completaron los 2 perIodos de estudio, La evaivaciOn de seguridad se realizó en todos los sujetos que recibieron al
menos 1 dosis durante el transcurso del estudio.

FarmacocinØtica (PK):
Se calcularon los siguientes parÆmetrosfarmacocinØticos para bupropion y sus metabolitos hidroxibupropion, treoamino alcohol de bupropion, eritroamino alcohol de bupropion y compuestos ponderados con actividad farmacoiógica (PAWC) mediante mØtodos estÆndarno compartimentales: AUCO-t, AUC0-inf, CmÆx,TmÆx,Kel, t, tiempo de residencia medio (MRT) y relación metabolito/original (M/P).

Seguridad:
Las incidencias para todos los episodios adversos (AEs) se tabularon por tratamiento y nümero de sujeto. TambiØn se documentaron los valores absolutos para signos vitales, parÆmetros de electrocardiogramas(ECG), parÆmetros delaboratorio y exÆmenesfisicos, y se sefialaron los valores por fuera del rango normal. Se tabularon los cambios con respecto a los valores de imnea base. Se documentaron los AEs utilizando tØrminos del investigador y del Diccionario Medico para Actividades de Regulación (MedDRA).

MØtodos estadIsticos:
Mediante ci uso de los procedimientos del Modelo Lineal General (GLM) en ci Sistema de AnÆlisis EstadIstico (SAS) se reaiizO elanÆiisisde variancia (ANOVA) en AUCO-t, AUCO-inf, y CmÆx in transformadosy en Kel, t, MRT y relación M/P no transformados en un nivel significativo de 0,05. Se calculó el coeficiente de variación (CV) intrasujeto medjante ci Error CuadrÆtico Medio (MSE) de latabla de ANOVA. La reiación de medias geomØtricas y el intervalo de confianza geomØtrica de 90% (C.I. de 90%) Se calcularon sobre la base de la diferencia en los Medios de MInimos Cuadrados de los

AUCO-t, AUCO-inf y CmÆx in transformados,entre la prueba y formulaciones de referencia. La TmÆx se analizó utilizando mØtodos no paramØtricos.

PARAMETROS FARMACOCINETICOS PARA BUPROPION:

ParÆnietros Media geomØtrica (%CV)
fannacocinØticos Media aritmØtica SD
2 x Comprimidos de 1 x Comprimido de
Bupropion HBr XL de 174 Bupropion HBr XL de 348
mg (A) (n=46) mg (B) (n46)
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AUCO-t (nghr/mL) 1523,91 (30,65)
1596,96 489,42

1493,80 (34,76)
1581,85 1549,92

AUCO-inf (nghr/mL) 1585,29 (30,09)
1658,90 499,09

1556,42 (34,03)
1644,75 559,69
Cmªx (ng/mL) 122,81 (32,48)
128,54–41,75

132,51 (37,22)
141,16–52,54
Tmx (hr) 5,00 (3,00-6,07) 5,00 (3,00-7,00)
t(hr) 23,65–7,36 23,84–6,90
Kel (hr-1)3,29E-02 1,28E-02 3,17E-02 9,78E-03
MRT(hr) 23,02–5,21 22,52–5,12
medio (mm - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA BUPROPION:

ParÆmetro Datos no corregidos de concentración
C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 96,48% a 107,86% 102,02% 16,01%
AUCO-inf 96,59% a 107,41% 101,85% 15,24%
CmÆx 86,68% a 99,10% 92,68% 19,29%
ParÆmetro Datos corregidos de concentración
C.I. de 90% RelaciOn de medias
AUCO-t 96,39% a 107,75% 101,91%
AUCO-inf 96,49% a 107,30% 101,75%
CmÆx 86,59% a 98,99% 92,58%

PARAMETROS FARMACOCINETICOS PARA HIDROXJBUPROPION:
ParÆmetros Media geomØtrica (%CV)
farmacocinØticos Media aritmØtica SD
2 x Comprimidos de 1 x Comprimido de
Bupropion H& XL de 174 Bupropion HBr XL de 348
mg (A) (n=46) mg (B) (n46)
AUCO-t (nghr/mL) 21175,12 (50,57) 20088,61 (60,27)
24691,89 12487,03 24435,37 14728,10
AUCO-inf(nghr/mL) 21601,69 (50,27) 20505,06 (59,96)

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25050,12::L 12593,05 24779,61 14857,90
Cmªx (ng/mL) 421,40 (46,88)
480,18+ 225,10

411,57 (50,75)
478,90 243,02
Tmªx (hr) 14,00 (5,00-24,00) 8,00 (5,00-24,00)
t (hr) 26,51 d: 5,77 26,05 6,24
Kel (hr-1) 2,75E-02 6,70E-03 2,83E-02 7,62E-03
MRT (hr) 43,58 8,67 42,84+9,32
RelaciónM/P 15,02–9,00 15,08–11,14
medio (min - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA HIDROXIBUPROPION:

ParÆmetro C.I. de 90% Relación de medias CVintrasujeto
AUCO-t 98,60% a 112,69% 105,41% 19,23%
AUCO-inf 98,62% a 112,54% 105,35% 19,01%
CmÆx 97,00% a 108,08% 102,39% 15,53%

PARAMETROS FARMACOCINETICOS PARA TREOAMINO ALCOHOL DE BUPROPION:
ParÆmetros
farmacocinØticos

Media geomØtrica (%CV)
Media aritmØtica SD

2 x Comprimidos de
Bupropion HBr XL de 174
mg (A) (n46)

1 x Comprimido de
Bupropion HBr XL de 348
mg (B) (n46)
AUCO-t (nghr/mL) 8720,28 (58,03)
9894,97 5741,81

8399,01 (53,61)
9441,77 5061,45
AUCO-inf (nghr/mL) 9433,66 (59,13)
10815,80 6395,02

9012,38 (54,93)
10252,40 5631,37
CmÆx (ng/mL) 157,76 (45,91)
171,83::L 78,89

161,36 (40,12)
173,35 69,55
TmÆx(hr) 8,00 (5,00-24,00) 6,00 (5,00-24,00)
t(hr) 56,77+20,15 53,97– 17,31
Kel (hr-1) 1,35E-02 4,44E-03 1,41E-02 4,58E-03
MRT (hr) 76,90 28,13 73,60 23,99
Relación M/P 6,65 4,37 6,43 3,94
medio (mm - max)
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EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA TREOAMINO ALCOHOL DE BUPROPION:

ParÆmetro C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 98,45% a 109,49% 103,83% 15,26%
AUCO-inf 99,20% a 110,45% 104,67% 15,42%
CmÆx 91,39% a 104,59% 97,77% 19,42%

PARAMETROS FARMACOCINETICOS PARA ERITROAMNO ALCOHOL DE BUPROPION:
Parametros
farmacocinØticos

Media geomØtrica (%CV)
Media aritmØtica SD
2 x Comprimidos de
Bupropion HBr XL de 174
mg (A) (n=46)

1 x Comprimido de
Bupropion HBr XL de 348
mg (B) (n=46)
AUCO-t (nghr/mL) 1624,49 (47,41)
1774,20 841,09

1556,84 (45,13)
1699,49 767,04
AUCO-inf(nghr/mL) 1713,80 (46,12)
1864,11 859,71

1663,28 (43,67)
1804,53 788,09
CmÆx (ng/mL) 29,54 (33,12)
30,79 10,20

29,01 (33,02)
30,40 10,04
TmÆx(hr) 14,00 (5,00-24,00) 13,00 (5,00-24,00)
t’/2 (hr) 32,71 7,84 32,51 8,78
Kel (hr-1)2,24E-02 5,24E-03 2,27E-02 5,72E-03
MRT (hr) 52,66 11,42 52,28 12,78
RelacjónM/P 1,16–0,68 1,13–0,50
medio (mill - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA ERITROAMINO ALCOHOL DE BUPROPION:

ParÆmetro C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 98,39% a 110,66% 104,35% 16,89%
AUCO-inf 97,25% a 109,16% 103,04% 16,60%
CmÆx 96,15% a 107,82% 101,82% 16,46%

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PARAMETROS FARMACOCINETICOS PARA PAWC:

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ParÆmetros Media geomØtrica (%CV)
farmacocinØticos Media aritmØtica SD
2 x Comprimidos de I x Cornprimido de
Bupropion HBr XL de 174 Bupropion HBr XL de 348
mg (A) (n46) mg (B) (n=46)
AUCO-t (iM.hr) 68,99 (39,40) 66,21 (47,37)
74,85 29,49 73,65 34,89
AUC0-inf(tMdi.r) 69,68 (39,62) 66,93 (47,56)
75,63 29,96 74,47 35,42
CmÆx(.iM) 1,60 (32,21) 1,64 (36,18)
1,68 0,54 1,76+-0,64
TmÆx(hr) 5,03 (4,00-14,00) 5,00 (4,00-24,00)
t (hr) 29,45 7,47 29,25 18,04
Kel (hr-1)2,55E-02 8,61E-03 2,56E-02 7,53E-03
MRT (lit) 44,38 8,96 43,99 9,89
medio (min - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA PARA PAWC:
ParÆmetro C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 98,43% a 110,30% 104,20% 16,36%
AUCO-inf 98,32% a 110,25% 104,12% 16,45%
CmÆx 91,74% a 102,73% 97,08% 16,26%

Conclusion:

El objetivo de este estudio fue evaluar la proporcionalidad de la concentración de la dosis de las dos concentraciones de comprimidos de Bupropion HBr XL (2 x 174 mg versus 1 x 348 mg) en sujetos masculinos y femeninos normales, saludables, no fumadores. Se evaluaron los datos de biodisponibilidad relativa del bupropion, sus metabolitos y los PAWC mediante la mediciOn y comparación de la exposiciOn pico y sistØmica total de los 2 tratamientos (utilizando AUCO-t, AUCO-inf y CmÆx). Losresultados estadisticos indicaron que las relaciones de niedias geomØtricas de prueba/referencia y los valores de los intervalos de confianza de 90% para AUCO-t, AUCO-inf y Cmªx de los datos de bupropion, sus metabolitos y los PAWC estuvieron dentro del rango de criterios de 80,00%- 125,00%. Basados en los resultados, se encontrO que los Comprimidos de Bupropion HBr XL (2 x 174 mg) y los Comprimidos de Bupropion HBr XL (1 x 348 mg) demostraron una exposición pico y sistØmica equivalente de bupropion y sus metabolitos

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cuando se administraron arnbas formulaciones en condiciones de ayuno. En conclusiOn, ’
se encontrO que los comprimidos de Bupropion XL de 174 mg (surninistrados como
2x1 74 mg) eran proporcionales en concentraciOn de la dosis a Los comprimidos de
Bupropion HBr XL de 348 mg. En general, los comprimidos de Bupropion HBr XL 174
5 mg (2 x 174 mg) y los comprimidos de Bupropion HBr XL de 348 mg fueron bien
tolerados como una dosis ünica de 348 mg, administrados en condiciones de ayuno, y no

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surgieron problemas de seguridad significativos.

Este estudio se realizó de conformidad con GCP.

Tabla: Parmetros farmacocinØticos medios (–SD) para Bupropion (n 46)
2x Comprimidos de lx Comprimido de
Bupropion HBr XL Bupropion HBr XL
del74mg de348mg
(06D029P) (06C1 59P)
(n=46) (n46)
AUCO-t 1597–489 1582+550
(ng hr/mL)
AUCO- 1659–499 1645– 560
(ng hr/mL)
Cmax(ng/mL) 128,5–41,8 141,2–52,5
TmÆx(hr) 5,0(3,0-6,1) 5,0(3,0-7,0)
t(hr) 23,7–7,4 23,8–6,9
MRT(hr) 23,0–5,2 22,5–5,1
Medio (rango)

Tabla: Resumen de estadIsticas para Bupropion (n = 46)

2 x Coinprimidos de Bupropion HBr XL de 174 mg
Versus lx Comprimido de Bupropion HBr XL de 348

Mg

Relación de medias Intervalo de confianza
geomØtricas geomØtrica de 90%
AUCO-t 102,02% 96,48 a 107,86%
AUCO- 101,85% 96,59 a 107,41%

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I Cmdx 92,68% 86,68 a 99,10%

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Tabla: ParÆmetrosfarmacocinØticos medios (+-SD) para Hidroxibupropion (n = 46)
2x Comprimidos de
Bupropion HBr XL
del74mg
(06D029P)
(n46)

lx Comprimido de
Bupropion HBr XL
de348mg
(06C1 59P)
(n=46)
AUCO-t (ng hr/mL) 24692-–12487 24435 –14728
AUCO- (ng hr/mL) 25050 –12593 24780– 14858
Cmx(ng/mL) 480,2–225,1 478,9–243,0
TmÆx (hr) 14,0 (5,0 - 24,0) 8,0 (5,0 - 24,0)
t(hr) 26,5–5,8 26,1–6,2
MRT(hr) 43,6–8,7 42,8–9,3
Relaciónmetabolito/
original

15,0– 9,0 15,1 11,1

Medio (rango)
Tabla: Resumen de estadIsticas para Hidroxibupropion (n = 46)

2 x Comprimidos de Bupropion HBr XL de 174 mg Versus lx Comprimido de Bupropion HBr XL de 348 mg

Relación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 105,41% 98,60 a 112,69%
AUCO- 105,35% 98,62 a 112,54%
CmÆx 102,39% 97,00 a 108,08%

Tabla: ParÆmetros farmacocinØticosmedios (–SD) para treoamino alcohol de bupropiori (n46)
2x Comprimidos de lx Comprimido de
Bupropion HBr XL Bupropion HBr XL
del74mg de348mg
(06D029P) (06C159P)
(n46) (n=46)

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AUCO-t(nghr/inL) 9895–5742 9442– 5061
AUCO- (ng hr/mL) 10816 –6395 10252– 5631
Cmax(ng/mL) 171,8–78,9 173,4–69,6
TmÆx(hr) 8,0 (5,0 - 24,0) 6,0 (5,0 - 24,0)
t (hr) 56,8 20,2 54,0 17,3
MRT(hr) 76,9–28,1 73,6–24,0
Relaciónmetabolito/
original

6,7+4,4 6,4–3,9

Medio (rango)

Tabla: Resumen de estadIsticas para treoamino alcohol de bupropion (n = 46)

2 x Comprimidos de Bupropion HBr XL de 174 mg
Versus lx Comprimido de Bupropion HBr XL de 348
mg

Relacjón de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 103,83% 98,45% a 109,49%
AUCO- 104,67% 99,20% a 110,45%
CmÆx 97,77% 91,39% a 104,59%

Tabla: ParÆmetrosfannacocinØticos medios (–SD) para eritroamino alcohol de bupropion (n=46)
2x Comprimidos de lx Comprimido de
Bupropion HBr XL Bupropion HBr XL
del74mg de348mg
(06D029P) (06C1 59P)
(n46) (n46)
AUCO-t(nghr/rnL) 1774– 841 1699+767
AUCO- (ng hr/mL) 1864– 860 1805– 788
CmÆx(ng/mL) 30,8–10,2 30,4–10,0
Tmªx (hr) 14,0 (5,0 24,0) 13,0 (5,0 24,0)
t(hr) 32,7+7,8 32,5–8,8

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MRT(hr) 52,7–11,4 52,3–12,8
Relación metabolito/
original

1,2 0,7 1,1 0,5

Medio (rango)

labia: Resumen de estadIsticas Para eritroamino alcohol de bupropion (n = 46)

2 x Comprimidos de Bupropion HBr XL de 174 mg
Versus lx Comprimido de Bupropion HBr XL de 348
mg

Relación de medias
geomØtricas

Intervaio de confianza
geomØtrica de 90%
AUCO-t 104,35% 98,39% a 110,66%
AUCO- 103,04% 97,25% a 109,16%
CmÆx 101,82% 96,15% a 107,82%

Tabla: ParÆmetrosfarmacocinØticos medios (–SD) Para PAWC (n = 46)
2x Comprimidos de lx Comprimido de
Bupropion HBr XL Bupropion HBr XL
ParÆmetros

del74mg de348mg
farmacocinØticos
(06D029P) (06C159P)
(n=46) (n=46)
AUCO-t QM hr) 74,9 29,5 73,7+-34,9
AUCO- (jiM hr) 75,6 30,0 74,5 35,4
CmÆx(jxM) 1,7–0,5 1,8–0,6
TmÆx(hr) 5,0 (4,0 14,0) 5,0 (4,0 24,0)
t (hr) 29,5 7,5 29,3 8,0
MRT(hr) 44,4–9,0 44,0–9,9
Medio (rango)
labia: Resumen de estadIsticas Para PAWC (n = 46)

2 x Comprimidos de Bupropion HBr XL de 174 mg
Versus lx Comprimido de Bupropion HBr XL de 348 mg

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Relación de medias
geornØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 104,20% 98,43 a 110,30%
AUCO- 104,12% 98,32 a 110,25%
CmÆx 97,08% 91,74a102,73%

Estudio de efecto por consumo de alimentos, con una Unica dosis, abierto, con doble intercambio de tratamiento de comprimidos de Bupropion HBr XL de 348 mg en sujetos masculinos y femeninos normales, saludables, no fumadores. Estudio B06-754PK-10121 (3229)

Se estudió el efecto del alimento en comprimidos de Bupropion HBr XL de 348 mg. La administraciOn de comprimidos de Bupropion HBr XL de 348 mg con alimentos dio
como resultado un aumento de la exposiciOn pico (CmÆx)y sistØmica (AUCO-t, AUCO-)
10 de bupropion de 7% y 19% respectivamente. La presencia de alimentos no condujo a
ningün cambio significativo en TmÆx. El aumento en CmÆxno fue significativo dado
que el intervalo de confianza (Cl) geomØtrico de 90% cayó dentro del rango de 80 a
125%. Los CI geomØtricos de 90% para AUCO-t y AUCO-c cayeron apenas afuera del
rango de 80 a 125% (CI de 90% para AUCO-t = 113,23 a 126,06%, para AUC0-0
15 112,96 a 125,52%). Este aumento minimo en AUC de bupropion con alimentos con
respecto al ayuno no plantearÆninguna preocupación en cuanto a la seguridad clinica
dado que el aumento del porcentaje estuvo entre –20% y ci limite superior del Cl geomØtrico de 90% fue aproximadamente 1% por encima del rango de aceptación.

20 Los resultados se muestran abajo y en las Figuras 44-49.

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Disefio de estudio y fase de desarrollo:
Estudio de fase I, de efecto por consumo de alimentos, con una ünica dosis, abierto, aleatoric, con doble intercambio de tratamiento.

Criterios principales a incluir:
Sujetos masculinos y femeninos normales, saludables, no fumadores en un rango de edades entre 18 y 55 afios.

30 Producto de pruebalproducto en investigación, nüinero de lote y via de administraciOn:

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Luego de una noche de ayuno de al menos 10 horas, y 30 minutos despuØs del comienzo
de una comida con alto contenido graso, 1 comprimido de Bupropion HBr XL 348 mg,
lote #: 06C159P, administrado por via oral con 240 mL de agua a temperatura ambiente.

5 Producto de referencia, nümero de lote y via de administración:
Luego de una noche de ayuno de al menos 10 horas, 1 comprimido de Bupropion HBr
XL de 348 mg, lote #: 06C159P, administrado por via oral con 240 mL de agua a temperatura ambiente.

10 Cantidad de sujetos (planificados y analizados):
En el PerIodo I hubo 48 sujetos dosificados. Todos los sujetos completaron el estudio, y
sus datos se utilizaron para los anªlisis farmacocinØticos y estadIsticos.

Tiempos de muestreo de extracción sanguinea:
15 Durante cada perIodo de estudio se recogieron 22 muestras de sangre de cada sujeto en
los siguientes tiempos de muestreo: 0,00 (dosis previa), 1,00, 2,00, 3,00, 4,00, 5,00, 6,00, 7,00, 8,00, 10,00, 12,00, 14,00, 16,00, 20,00, 24,00, 36,00, 48,00, 60,00, 72,00, 120,00, 168,00, y 216,00 horas dosis posterior.

20 Procedimiento bioanalitico:

El bupropion, eritroamino alcohol de bupropion, treoamino alcohol de bupropion, hidroxibupropion, y el estÆndar interno, 1 -(3-clorofenil)-piperazina,se extraj eron
mediante extracción de fase sólida en un medio orgªnico de 0,50 mL de plasma humano.
Se inyectó una alicuota de este extracto en un sistema cromatogrÆficolIquido de alto
025 rendimiento y se detectó utilizando un espectrómetro de masa en tandem. Se separaron
los analitos mediante cromatografla de fase reversa. La evaluaciOn del contenido se llevó
a cabo mediante la construcción de una curva de calibración de ocho (8) puntos (con
exclusion de concentración cero) que cubre el rango de 1,000 ng/mL a 1023,900 ng/mL
(en plasma humano) para bupropion, 1,000 ng/mL a 1023,900 ng/mL (en plasma
30 humano) para eritroamino alcohol de bupropion, 1,000 ng/mL a 1023,900 ng/mL (en
plasma humano) para treoamino alcohol de bupropion y 3,906 ng/mL a 3999,600 ng/mL
(en plasma humano) para hidroxibupropion. La pendiente y la interceptación de las
curvas de calibraciOn se determinaron mediante anÆlisis deregresión lineal pesado
(1/area pico2). Se analizaron dos curvas de calibración y muestras QC por duplicado (en
35 tres niveles de concentración) junto con cada lote de las muestras de estudio. Las
relaciones de area pico se utilizaron para determinar la concentración de los estÆndares,

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las muestras de control de calidad y las muestras de estudio desconocidas de las curvas de calibración.

Criterios para la evÆluación:
El anÆlisisfannacocin&ico se realizó en 48 sujetos que completaron los 2 perIodos de
estudio. La evaluación de seguridad se realizó en todos los sujetos que recibieron al
menos 1 dosis durante el transcurso del estudio.

FarmacocinØtica (PK):
10 Se calcularon los siguientes parÆmetros farmacocinØticos para bupropiony sus metabolitos hidroxibupropion, treoamino alcohol de bupropion, eritroamino alcohol de bupropion y PAWC mediante mØtodos estÆndarno compartimentales: AUCO-t, AUCO-
inf, CmÆx, TmÆx, Kel,t, MRT y relaciOn M/P.

15 MØtodos estadisticos:

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Mediante el uso de los procedimientos del Modelo Lineal General (GLM) en ci Sistema
de AnÆlisis Estadfstico(SAS) se realizó el anÆlisisde variancia (ANOVA) en AUCO-t, AUCO-inf y CmÆx Intransformados y en Kel, t, MRT y relación M/P no transformados
en un nivel significativo de 0,05. Se calculó el coeficiente de variación (CV) intrasujeto mediante el Error CuadrÆtjco Medio(MSE) de la tabla de ANOVA. La relación de
medias geomØtricas y ci intervalo de confianza geomØtrica de 90% (Cd. de 90%) se caleularon sobre la base de la diferencia en los Medios de MInimos Cuadrados de los AUCO-t, AUCO-inf y CmÆxIn transformados, entre la prueba y formulaciones de referencia. La Tmªx se analizó utilizando mØtodos no paramØtricos.

Resumen de resultados farmacocinØticas:
PARAMETROS FARMACOC1NETICOS PARA BUPROPION:
ParÆmetros Media geomØtrica (%CV)
farmacocinØticos Media aritmØtica SD
Comprimidos de Bupropion Comprimidos de Bupropion
FIBr XL de 348 mg (A) HBr XL de 348 mg (B)
(Alimentados) (n48) (Ayuno) (n=48)
AUCO-t 1743,38 (29,91) 1459,22 (27,36)
(ngthr/mL) 1813,67 542,56 1514,68 414,40
AUCO-inf 1806,08 (29,34) 1516,77 (26,77)
(nghr/mL) 1876,44 550,60 1572,10 420,91
Cmªx 130,36 (31,47) 121,28 (27,41)

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(ng/mL) 136,80–43,05 125,91–34,52
TmÆx(hr) 5,00 (2,00-10,00) 5,00 (3,00-7,00)
t112 (hr) 23,19–6,45 21,29–6,65
Kel (hr-1) 3,27E-02 1,1OE-02 3,60E-02 1,17E-02
MRT(hr) 22,36–5,92 21,20–5,56
medio (min - max)
EVALUACIONES DE BIODISPONIBILIDAD RELATIVA (ALIMENTADO/EN AYUNO) PARA BUPROPION:
ParÆmetro C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 113,23% a 126,06% 119,47% 15,75%
AUCO-inf 112,96% a 125,52% 119,07% 15,47%
CmÆx 98,20% a 117,64% 107,48% 26,83%

PARAMETROS FARMACOCINETICOS PARA HIDROXIBUPROPION: ParÆmetros
farmacocinØticos

Media geomØtrica (%CV)
Media aritmØtica SD
Comprimidos de Bupropion
HBr XL de 348 mg (A)
(Alimentados) (n48)

Comprimidos de Bupropion
HBr XL de 348 mg (B)
(Ayuno) (n48)
AUCO-t

(nghr/mL)

21556,18 (54,71)
25505,66 113953,00

21143,44 (53,45)
24948,49 13334,10
AUCO-inf
(ng.hr/mL)

22061,74 (54,24)
25 870,62 14032,96

21628,02 (52,78)
25284,90 13 346,59
CmÆx

(ng/mL)

457,15 (45,58)
525,08:1- 239,34

445,93 (43,57)
507,42 221,07
TmÆx(lit) 14,00 (7,00-36,00) 8,00 (5,00-24,02)
t1/2(hr) 24,77–4,81 24,28–4,92
Kel (hr-1) 2,90E-02 5,59E-03 2,97E-02 5,93E-03
MRT(hr) 42,65–7,61 41,13–7,37
RelaciónM/P 13,17–5,96 15,48–7,32
medio (min - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA (ALIMENTADO/EN
10 AYUNO) PARA HIDROXIBUPROPION:
ParÆmetro Cd, de 90% [Relación de medias CV intrasujeto

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AUCO-t 95,40% a 108,96% 101,95% 19,58%
AUCO-inf 95,50% a 108,95% 102,01% 19,41%
CmÆx 96,75% a 108,62% 102,52% 17,00%

PARAMETROS FARMACOCINETICOS PARA TREOAMINO ALCOHOL DE BUPROPION:
ParÆmetros
farmacocinØticos

Media geomØtrica (%CV)
Media aritmØtica SD
Comprimidos de Bupropion
HBr XL de 348 mg (A)
(Alimentados) (n=48)

Comprimidos de Bupropion
HBr XL de 348 mg (B)
(Ayuno) (n=48)
AUCO-t

(nghr/mL)

9430,21 (53,90)
10454,75 5635,07

8355,97 (53,13)
9356,36 4971,39
AUCO-inf
(nghr/mL)

9970,03 (54,94)
11148,70 6124,76

8875,08 (55,60)
10081,16 5604,76
CmÆx

(ng/mL)

179,62 (43,15)
193,84–83,63

154,88 (41,45)
168,36–69,79

Tmªx (hr)* 11,00 (5,00-36,00) 7,00 (5,00-24,00)
t112 (hr) 50,49–15,20 50,82–18,50
Kel (hr-1)1,49E-02 4,29E-03 1,51E-02 4,44E-03
MRT (hr) 69,31 20,00 70,03 23,78
RelaciónM/P 5,94–2,85 6,35–3,21
* medio - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA (ALIMENTADO/EN AYUNO) PARA TREOAMINO ALCOHOL DE BUPROPION:
ParÆmetro C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 106,31% a 119,80% 112,86% 17,56%
AUCO-inf 105,67% a 119,42% 112,34% 17,99%
CmÆx 107,44% a 125,18% 115,97% 22,58%

10 PARAMETROS FARMACOCINETICOS PARA ERITROAMINO ALCOHOL DE BUPROPION;
ParÆmetros Media geometrica (%CV)
farmacocinØticos Media aritmØtica – SD

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Comprimidos de Bupropion Comprimidos de Bupropion
HBr XL de 348 mg (A) HBr XL de 348 mg (B)
(Alimentados) (n=48) (Ayuno) (n48)
AUCO-t 1827,80 (41,59) 1602,42 (43,32)
(ngthr/mL) 1976,58 822,09 1762,94 763,75
AUCO-inf 1922,92 (40,33) 1701,69 (41,91)
(nghr/mL) 2069,29 834,50 1860,34 779,59
CmÆx 33,52 (29,90) 28,94 (29,09)
(ng/mL) 34,90–10,44 30,18–8,78
TmÆx(hr) 14,00 (8,00-36,00) 14,00 (5,00-36,00)
tl/2(hr) 31,81–7,32 31,09–7,84
Kel (hr-1) 2,28E-02 4,82E-03 2,36E-02 5,60E-03
MRT(hr) 53,31–11,39 51,58–11,29
RelaciónM/P 1,11+0,38 1,18–0,42
medio - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA (ALIMENTADO/EN AYUNO) PARA ERITROAMINO ALCOHOL DE BUPROPION:
ParÆxnetro Cd. de 90% Relación de medias CV intrasujeto
AUCO-t 106,29% a 122,40% 114,07% 20,81%
AUCO-inf 105,83% a 120,66% 113,00% 19,32%
CmÆx 108,36% a 123,83% 115,84% 19,66%

PARAMETROS FARMACOCINITICOS PARA PAWC:
ParÆmetros Media geomØtrica (%CV)
farniacocinØticos Media aritmØtica SD
Comprimidos de Bupropion Comprimidos de Bupropion
HBr XL de 348 mg (A) HBr XL de 348 mg (B)
(Alimentados) (n=48) (Ayuno) (n=48)
AUCO-t 71,68 (45,24) 68,31 (44,26)
(iM.hr) 78,53 – 35,52 74,80 33,11
AUCO-inf 72,09 (45,62) 68,78 (44,28)
(jiM.hr) 79,05 36,07 75,31 33,34
cmdx 1,65 (34,28) 1,67 (31,70)

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GM) 1,75–0,60 1,75–0,55
TmÆx(hr)* 10,00 (2,00-24,00) 5,51 (4,00-24,00)
tl/2(hr) 26,39–6,17 26,33–7,38
Kel (hr-1) 2,78E-02 6,83E-03 2,81E-02 6,72E-03
MRT(hr) 42,31–7,70 41,45–8,44

* medio (mm - max)

EVALUACIONES DE BIODISPONIBILIDAD RELATIVA (ALIMENTADO/EN AYUNO) PARA PAWC:
ParÆmetro C.I. de 90% Relación de medias CV intrasujeto
AUCO-t 98,67% a 111,60% 104,94% 18,11%
AUCO-inf 98,47% a 111,56% 104,81% 18,36%
CmÆx 92,74% a 105,44% 98,89% 18,89%

Conclusion:

El objetivo de este estudio fue evaluar el efecto de los alimentos en la velocidad y el alcance de absorción del bupropion a partir de una formulación nueva de Comprimidos de Bupropion HBr XL (liberación extendida) de 348 mg.

Se evaluaron los datos de biodisponibilidad relativa del bupropion, sus metabolitos y los compuestos ponderados con actividad farmacológica (PAWC) mediante la medición y comparación de la exposición pico y sistØmica total de los 2 tratamientos (utilizando AUCO-t, AUCO-infy CmÆx).

Con respecto a la administraciOn de fÆrmacosen condiciones de ayuno, la exposición pico y sistØmica para bupropion con una dosis oral ünica de Comprimido de Bupropion HBr XL de 348 mg con alimentos aumentó 7% y 19% respectivamente. El aumento en Cmax no fue significativo dado que el intervalo de confianza geomØtrico de 90% cayó dentro del rango de 80,00 -125,00%. Sin embargo, el Cl de 90% para AUCO-t y AUCO-infcayó apenas afuera del rango de 80,00 - 125,00% (Cl de 90% para AUCO-t = 113,23
- 126,06%, Cl de 90% para AUCO-inf= 112,96 - 125,52%). Se concluyO que esta falla minima de no estar dentro de los 80,00% - 125,00% no era significativa clinicamente. Finalmente, la presencia de alimentos no condujo a ningün cambio en TmÆxde bupropion.

Se observaron resultados similares con hidroxibupropion, eritroamino alcohol de bupropion y treoamino alcohol de bupropion.

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Para los PAWC, los alimentos no tuvieron una influencia signifleativa en ci CmÆxy los
AUC ya que ci CI de 90% cayó dentro del rango de % de 80,00-125,00%.

En conclusion, se infiriO que los Comprimidos de Bupropion HBr XL de 348 mg no presentan un efecto significativo por consuino de alimentos wando se los suministra en una dosis oral ünica.

En general, los comprimidos de Bupropion HBr XL de 348 mg fueron bien tolerados cuando se administraron en una dosis niea de 348 mg en condiciones de alimentaciOn y de ayuno y no surgieron probiemas de seguridad significativos.

Este estudio se realizO de conformidad con GCP.

Tabia: ParÆmetros farmacocinØticos medios(-LSD) para Bupropion (n = 48)
Alimentado Ayuno
Comprimidos de Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de348mg de348mg
(06C159P) (06C159P)
(n48) (n=48)
AUCO-t 1814–543 1515–414

(ng hr/mL)
AUCO-co 1876– 551 1572 –421

(ng hr!mL)
Cmax(ng/mL) 136,8–43,1 125,9–34,5
TmÆx (hr) 5,0 (2,0 - 10,0) 5,0 (3,0 - 7,0)
t(hr) 23,2–6,5 21,3–6,7
MRT(hr) 22,4+5,9 21,2–5,6
Medio (rango)

Tabla: Resumen de estadisticas para Bupropion (n = 48)

Comprimidos de Bupropion HBr XL de 348 mg: Alirnentado versus en ayuno

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Relación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 119,47% 113,23 a 126,06%
AUCO- 119,07% 112,96 a 125,52%
CmÆx 107,48% 98,20 a 117,64%

Tabla: ParÆmetros farmacocinØticos medios (–SD) para. Hidroxibupropion(n = 48)
Alimentado Ayuno
Comprimidos de Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de348mg de348mg
(06C159P) (06C159P)
(n=48) (n=48)
AUCO-t (nghr/mL) 25506 –13953 24948 –13334
AUCO- (ng hr/mL) 25871– 14033 25285 –13347
CmÆx (ng/mL) 525,1 – 239,3 507,4 – 221,1
TmÆx (hr) 14,0 (7,0 - 36,0) 8,0 (5,0 24,0)
t(hr) 24,8–4,8 24,3–4,9
MRT(hr) 42,7–7,6 41,1–7,4
Relación metabolito/ 13,2 – 6,0 15,5 7,3
original
Medio (rango)

Tabla: Resumen de estadisticas para. Hidroxibupropion (n = 48)

Comprimidos de Bupropion HBr XL de 348 mg:
Alimentado versus en ayuno

Relación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 101,95% 95,40 a 108,96%
AUCO- 102,01% 95,50 a 108,95%
CmÆx 102,52% 96,75 a 108,62%

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2.
Tabla: ParÆmetrosfarmacocinØticos medios (-–-SD) para treoamino alcohol de bupropion (n=48)
Alimentado Ayuno
Comprimidos de Cornprimidos de
Bupropion HBr XL Bupropion HBr XL
de348mg de348mg
(06C159P) (06C159P)
(n48) (n=48)
AUCO-t (ng hr/mL) 10455–5635 9356–4971
AUCO- (ng hr/mL) 11149– 6125 10081–5605
Cmax(ng/mL) 193,8–83,6 168,4–69,8
TmÆx(hr) 11,0(5,0-36,0) 7,0(5,0-24,0)
t(hr) 50,5–15,2 50,8–18,5
MRT (hr) 69,3 – 20,0 70,0 – 23,8
Relaeión metabolito! 5,912,9 6,4 – 3,2
original
Medio (tango)

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Tabla: Resumen de estadIsticas para treoamino alcohol de bupropion (n = 48)

Comprimidos de Bupropion HBr XL de 348 mg:
Alimentado versus en ayuno

Relación de medias
geomØtricas

Intervalo de conflauza
geomØtrica de 90%
AUCO-t 112,86% 106,31 a 119,80%
AUCO- 112,34% 105,67 a 119,42%
CmÆx 115,97% 107,44a125,18%

Tabla: ParÆmetrosfarmacocinØticos medios (–-SD) para eritroamino alcohol de bupropion (n48)
Alimentado Ayuno
Comprimidos de Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de348mg de348mg
(06C159P) (06C159P)
(n=48) (n=48)
AUCO-t (ng hr/mL) 1977+822 1763+764
AUCO- (ng hr/mL) 2069 835 1860– 780
Cmax(ng/mL) 34,9–10,4 30,2–8,8
TmÆx(hr) 14,0 (8,0 36,0) 14,0 (5,0 36,0)
t(hr) 31,8–7,3 31,1–7,8
MRT(hr) 53,3–11,4 51,6–11,3
Relación metabolito! 1,110,4 1,2:L 0,4
original
Medio (rango)

Tabla: Resumen de estadfsticas para eritroamino alcohol de bupropion (n = 48)

Comprimidos de Bupropion HBr XL de 348 mg:
Alimentado versus en ayuno

Relación de medias Intervalo de confianza geomØtricas geomØtrica de 90%

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AUCO-t 114,07% 106,29 a 122,40%
AUCO- 113,00% 105,83 a 120,66%
CmÆx 115,84% 108,36 a 123,83%
Tabla: ParÆmetrosfarrnacocinØticos medios (+SD) para PAWC (n = 48)
’Alimentado Ayuno
Comprimidos de Comprimidos de
ParÆmetros Bupropion HBr XL Bupropion HBr XL
farmacocinØticos de 348 mg de 348 mg
(06C159P) (06C159P)
(n=48) (n=48)
AUCO-t(.xMhr)) 78,5–35,5 74,8–33,1
AUCO- (.xM hr)) 79,1 36,1 75,3 33,3
CmÆxQ.tM) 1,8–0,6 1,8–0,6
TmÆx (hr) 10,0 (2,0 - 24,0) 5,5 (4,0 24,0)
t(hr) 26,4–6,2 26,3+7,4
MRT(hr) 42,3–7,7 41,5–8,4
Medio (rango)

Tabla: Resumen de estadIsticas para PAWC (n = 48)

Comprimidos de Bupropion HBr XL de 348 mg:
Alimentado versus en ayuno

Relación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 104,94% 98,67 a 111,60%
AUCO- 104,81% 98,47 a 111,56%
CmÆx 98,89% 92,74 a 105,44%

Estudio de proporcionalidad de la concentraciOn de la dosis, en estado estacionario, en ayunas, con doble intercambio de tratamiento de comprimidos de Bupropion HBr XL
(522 mg vs. 3x174 mg) en sujetos adultos voluntarios, saludables, no fumadores. Estudio
10 1B06-802PK-10121 (AA40055)

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Se estudiaron la velocidad y el alcance de absorciOn de un Comprimido de Bupropion
HBr XL de 522 mg en relación con 3 x comprimidos de Bupropion HBr XL de 174 mg
en condiciones de ayuno con varias dosis. El comprimido de 522 mg fue equivalente a los comprimidos de 174 mg administrados en 3 x 174 mg.

Los resultados se muestran abajo y en las Figuras 50-54.

Metodologla:
Este fue un estudio de proporcionalidad de concentraciOn de la dosis, de varias dosis, de
10 doble secuencia, con doble intercambio de tratamiento, aleatorio, abierto, en condiciones
de ayuno.

. Cantidad de sujetos (planifleados y analizados):
Se administró la dosis a un total de 40 sujetos saludables no fumadores (29 masculinos y
15 11 femeninos), 29 de los cuales (21 masculinos y 8 femeninos) completaron el estudio.
Se calcularon parÆmetrosfarmaeocinØticos para los sujetos que compietaron el estudio.
Se realizó una evaluación de seguridad para todos los sujetos que recibieron al menos una
dosis.

20 Criterios principales a incluir y excluir:
HabrIan de seleecionarse para incluir en el estudio cuarenta (40) adultos saludables no fumadores (por 3 meses al menos), masculinos y femeninos voluntarios en un rango entre 18y55aflos.

25 Productos de prueba y de referencia, dosis, via de administración y nt’imero de lote:
Comprimidos de Bupropion HBr XL de 522 mg (producto de prueba), fabricados por
Biovail Corporation;
N° de lote: 06M1 19P; N° de lote a granel: 06M303.

30 Comprimidos de Bupropion HBr XL de 174 mg (producto para dosificación y producto
de referencia), fabricado por Biovail Corporation; N° de lote: 06M062P; No de lote a granel: 06D117.

Duración del tratamierito:

35 El estudio implicó un perlodo de dosifieaeiOn progresiva de 8 dias previo al periodo de
tratamiento. En las mafianas de los dias 1 a 3 se administró a todos los sujetos una dosis
de un comprimido (1 x 174 mg; producto de referenda) con 240 mL de agua a

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temperatura ambiente, en condiciones de ayuno. En las mafianas de los dias 4 a 8 se administró a todos los sujetos una dosis de dos comprimidos (2 x 174 mg; producto de referencia para una dosis total de 348 mg) con 240 mL de agua a temperatura ambiente,
en condiciones de ayuno.
5

Durante 14 dlas consecutivos (dlas 9 a 22) los sujetos recibieron un comprimido de bromhidrato de bupropion de 522 mg (producto de prueba) o tres comprimidos de bromhidrato de bupropion de 174 mg (producto de referencia para una dosis total de 522 mg). En las mafanas de los dIas 23 a 36 los sujetos recibieron el tratamiento alternativo.
10 No hubo lavado entre los tratamientos. Los sujetos fueron dosificados en condiciones de
ayuno.

Criterios para la evaluación:
Los puntos finales del estudio fueron los intervalos de confianza de 90% de las relaciones
15 de medios de mInimos cuadrados (LSM) para los parÆmetros farmacocinØticas AUCO-,
CmÆx,ssy Cmln,ss de la prueba para formulación de referencia en condiciones de ayuno.

La evaluación de seguridad incluyó evaluaciones de laboratorio, pruebas de sedación,
pruebas neurológicas, exÆmenes fisicos, episodios adversos, control ECU y evaluaciones
20 de signos vitales.
FarmacocinØtica:
Se realizO un anÆlisisfarmacocinØtico usando anÆlisis nocompartimental. Se calcularon
los siguientes parÆmetros: AUCO,CmÆx,ss, TmÆx,ss,Cpd, Cmin,ss, Cssav, % de fluctuación y % de oscilación para bupropion, hidroxibupropion, treoamino alcohol de
1025 bupropion y eritroamino alcohol de bupropion.

TambiØn se calcularon todos los parÆmetrosfarmacocinØticos para los compuestos ponderados con actividad farmacológica (PAWC).

30 AdemÆs se calcularon lasrelaciones metabolito/original (M/P) basadas en AUCO
corregido para peso molecular para todos los metabolitos.

Seguridad:
Se resumieron los datos de seguridad, incluidos evaluaciones de laboratorio, exÆmenes
35 flsicos, episodios adversos, control ECG y evaluaciones de signos vitales por tiempo de
recolección y por grupo de tratamiento, cuando fue adecuado. Se calcularon las
estadisticas descriptivas (media aritmØtica, desviaciOn estÆndar, media,minima y

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maxima) para datos de seguridad cuantitativos asI como para la diferencia desde la lfnea base, si correspondia. Se compilaron las unidades de frecuencia para la clasificación de los datos de seguridad cualitativos. AdemÆs, se suministró una tabla de cambios en la que
se describen los cambios de intervalo fuera de lo normal para los resultados de
laboratorio clinico. TambiØn se presentO una tabla de cambios normales-anormales para examen fisico y resultados de LEG.

Se codificaron los episodios adversos utilizando la Ultima version del diccionario
MedDRA y se resumieron por tratamiento para la cantidad de sujetos que informaron del
10 episodio adverso y la cantidad de episodios adversos informados. Se suministró un
listado de datos de episodios adversos por sujeto que incluyó perIodo del investigador,
grupo de tratamiento, gravedad y relación con el tratamiento. Se hizo una lista de
medicamentos concornitantes por sujeto y se codificó utilizando la ültima version del
- diccionario de fÆrmacosde la OMS. La historia clInica se ordenó por sujeto y se codificó
15 utilizando la ültima version del diccionario MedDRA.

MØtodos estadisticos:

Se realizaron estadIsticas descriptivas para concentraciones de plasma y para todos los parÆmetros farmacocinØticos.Utilizando el procedimiento de GLM en SASfi se realizó
20 un anÆlisis devariancia (ANOVA) en parÆmetros farmacocinØticosin-transformados
AUCO-, CmÆx,ssy CmIn,ss. Se calculO el coeficiente de variación (CV) intrasujeto
mediante el Error CuadrÆtico Medjo (MSE) delANOVA. Se calcularon las relaciones de LSM y los intervalos de confianza de 90% basados en la diferencia en el LSM de los
AUCO-, CmÆx,ssy CmIn,ss In-transformados entre la prueba y la formulaciOn de
25 referencia. Se evaluO el estado estacionario utilizando concentraciones de dosis previas
en los dIas 19, 20, 21 y 22 asI como en los dias 33, 34, 35 y 36 basado en los contrastes
de Helmert. Se evaluO la biodisponibilidad sobre la base de los intervalos de confianza de 90% de las relaciones de LSM de la prueba para formulación de referencia para el
fÆrmaco original,metabolitos y PAWC. Los porcentajes del intervalo de con–ianza
30 estuvieron dentro del criterio de aceptación de 80,0 - 125,0%.

Se analizó el parÆmetroTmÆx,ssutilizando mØtodos no paramØtricos de Koch y
Hauschke. Se evaluó la igualdad del efecto del tratamiento en ambas secuencias
utilizando las pruebas de Wilcoxon para muestras independientes. Se estimó el cambio
35 entre los dos tratamientos mediante el cªlculo objetivo de media de Hodges-Lehmann y
su intervalo de confianza de 90%. El procedimiento de Hodges-Lehmann amplIa la
prueba de Wilcoxon para muestras independientes para proporcionar un cÆlculo delpunto

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objetivo medio y un intervalo de confianza para la magnitud del cambio entre dos
poblaciones.

Resumen / resultados:
Bupropion
Los parÆmetrosfarmacocinØticos del bupropion en plasma segün administraciones orales de comprimidos de Bupropion HBr XL de 522 mg y comprimidos de Bupropion HBr XL de 174 mg (dosis total de 522 mg) son los siguientes:

ParÆmetro Comprimido de Bupropion
HBr XLlx522mg

Comprimidos de Bupropion
HBr XL3xl74mg
Media geomØtrica (%CV)
AUCO (ngh!mL)
CmÆx,ss(ng/mL)
Cmfn,ss (ng/mL)

1655 (32,4%) 1677 (33,0%)
165(37,2%) 159(32,0%)
28,8 (44,6%) 28,9 (41,4%)
TmÆxmedia (Min
TmÆx,ss (h) 4,00 (2,00 7,00) 5,00 (3,00 6,06)
Media aritmØtica (– SD)
AUCO(nghlmL)
CmÆx,ss(nglmL)
CmIn,ss (ng/mL)
Cssprorn(nglmL)
Fluctuación (%)
Oscilación (%)

1730–494 1763–574
176+63,6 167–53,0
31,4 13,4 31,3 13,2
72,1–20,6 73,5+23,9
200 48,6 187-+24,9
522 251 468 1143

En estado estacionario, el alcance y la velocidad media de la exposiciOn sistØmica del bupropion dentro de un intervalo de dosificación de 24 horas (CrnÆx,ss, AUCO) fueron similares entre el comprimido de Bupropion HBr XL 1 x 522 mg y los comprimidos de Bupropion HBr XL 3 x 174 mg. Los valores de fluctuación de % medio y de oscilación de % medio fueron 7% y 12% respectivamente, mayor para el comprimido de Bupropion HBr XL 1 x 522 mg comparado con los comprimidos de Bupropion HBr XL 3 x 174 mg.

El valor de TmÆx,ssmedio de bupropion fue de 4,0 horas y 5,0 horas para los comprimidos de Bupropion HBr XL 1 x 522 mg y Bupropion HBr XL 3 x 174 mg respectivamente. El intervalo de confianza de 90% no paramØtrico para el TmÆx,ss medio

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de la diferencia prueba - referencia (efecto de formulaciOn) fue [-1,00; 0,50] para
bupropion.

Los resultados de la ANOVA para bupropion en plasma segün administraciones orales de
5 un comprimido de Bupropion HBr XL 1 x 522 mg y comprimidos de Bupropion HBr XL
3 x 174 mg (dosis total de 522 mg) son los siguientes:

Relaciones de LSM (Intervalos de confianza de 90%)
ParÆmetro Comprimido de Bupropion HBr XL de
Biovail 1 x 522 mg (A) vs.. Comprimidos
de Bupropion HBr XL de Biovail 3 x 174
mg (B)
AUCO- 97,8% (91,4% -104,5%)
CmÆx,ss 103,2% (96,0% 111,0%)
CmIn,ss 99,0% (90,7% 108,0%)

10 Los intervalos de confianza de 90% de la relación de LSM derivada de los anÆlisisde los
parÆmetrosfarmacocinØticos in-transformados AUCO-, CmÆx,ssy Cmmn,ss para
bupropion en plasma estuvieron entre 80,0-125,0%.

Los resultados de contrastes de Helmert demostraron que la biodisponibilidad relativa
15 para bupropion para ambos comprimidos de concentraciôn de la dosis (1 x 522 mg y 3 x
174 mg) fue evaluada en condiciones de estado estacionario los dias 22 y 36.

Metabolitos de bupropion
Los parÆmetrosfarmacocinØticos de los metabolitos de bupropion en plasma segün
20 administraciones orales de un comprimido de Bupropion HBr XL 1 x 522 mg y
comprimidos de Bupropion HBr XL 3 x 174 mg (dosis total de 522 mg) son los
siguientes.

ParÆmetro ’Hidroxibupropion Treoamino alcohol de Eritroamino alcohol de
bupropion bupropion
Bupropion Bupropion Bupropion Bupropion Bupropion Bupropion
HBr XL HBr XL HBr XL HBr XL HBr XL HBr XL
1x522 3x174 1x522 3x174 1x522 3x174
mg mg mg mg mg mg

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Media
geomØtrica
(% CV)
AUCO-’t 25158 25271 13802 13658 2857 2831

(nghlmL) (53,4%) (48,5%) (40,2%) (40,7%) (38,0%) (36,5%) CmÆx,ss 1338 1311 753 731 146 144 (ng/mL) (48,5%) (42,9%) (38,3%) (39,6%) (35,8%) (36,9%), CmIn,ss 880 943 450 466 101 105 (ng/mL) (57,7%) (54,5%) (48,7%) (40,8%) (48,2%) (36,7%) TmÆxmedio
(Min-MÆx)
TmÆx,ss (h)
5,04 7,00 6,00 7,00 6,00 8,00
(2,00- (3,00- (2,03- (3,00- (2,00- (3,00-
8,00) 12,00) 10,00) 14,00) 10,00) 16,00)
Media
aritmØtica (–
SD) 27738– 27389– 148401 14730– 30481 3006–
AUCO-t 10583 9385 5929 6138 1135 1075
(nghlmL) 1457– 1402– 805+309 785 –311 155+55,4 154–54,9
CmÆx,ss 530 446
(ng/mL) 986–415 1042– 496–220 504–218 111–46,5 112–40,8
Cmfn,ss 410
(ng/mL) 1156– 1141– 618–247 614+256 127–47,3 125 –44,8
Cssprom 441 391
(ng/mL) 43,0– 34,9– 52,1– 46,7– 37,1– 33,5–
Fluctuación 17,3 15,4 19,0 13,3 17,0 12,6
(%) 55,1– 40,5– 71,9– 58,3– 47,3+ 38,6+
Oscilación 32,8 20,8 45,3 20,3 32,9 16,9
(%) 15,7– 16,0– 8,65– 8,47+ 1,81– 1,77–
Relación 6,82 8,35 2,70 2,83 0,599 0,610
M/P

En estado estacionario, las relaciones metabólicas basadas en ci AUCO- de hidroxibupropion, treoamino alcohol de bupropion y eritroamino alcohol de bupropion sobre bupropion fueron 15,7, 8,65 y 1,81 respectivamente para ci comprimido de
5 Bupropion HBr XL de Biovail 1 x 533 mg. Las relaciones metabólicas fueron simulares 317

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cuando se las comparO con comprimidos de Bupropion HBr XL de Biovail de 3 x 174

Mg.

Los valores de fluctuación de % medio y de oscilación de % medio de todos los
metabolitos de bupropion fueron comparables segün ambos comprimidos de concentración de la dosis (comprimidos de 1 x 522 mg y 3 x 174 mg)

El valor TmÆx,ss medio de hidroxibupropiony eritroarnino alcohol de bupropion Se observO 2 horas antes para el comprimido de Bupropion HBr XL 1 x 522 mg que para los comprimidos de Bupropion HBr XL 3 x 174 mg. El valor TmÆx,ssmedio de treoamino alcohol de bupropion se observó 1 hora antes para el comprimido de Bupropion HBr XL 1 x 522 mg que para los comprimidos de Bupropion HBr XL 3 x 174 mg. Los intervalos de confianza de 90% no paramØtricos para el TmÆx,ss mediode la diferencia prueba - referencia (efecto de formulación) fueron [-2,00; 0,00] para hidroxibupropion, [-2,00; - 0,50] para treoamino alcohol de bupropion y [-2,00; 0,00] para eritroamino alcohol de bupropion.

Los resultados farmacocinØticos de los metabolitos de bupropion en plasma segün administraciones oraTes de comprimidos de Bupropion HBr XL 1 x 522 mg y Bupropion HBr XL 3 x 174 mg (dosis total de 522 mg) son los siguientes.

Relacjones de LSM (Intervajos de confiariza de 90%)
ParÆmetro Hidroxibupropion Treoamino alcohol Eritroamino alcohol
de bupropion de bupropion
Comprimidos de
Comprimidos de Comprimidos de Bupropion HBr XL
Bupropion HBr XL Bupropion HBr XL de Biovail 1 x 522
de Biovail 1 x 522 de Biovail 1 x 522 mg (A) vs..
mg (A) vs.. mg (A) vs.. Bupropion HBr XL
Bupropion HBr XL Bupropion HBr XL de Biovail 3 x 174
de Biovail 3 x 174 de Biovail 3 x 174 mg (B)
mg (B) mg (B)

AUCO- 99,5% 100,9% 100,7%
(95,3% 104,0%) (94,1% 108,1%) (94,6% 107,2%)

CmÆx,ss 102,2% 102,6% 101,0%

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(98,0%- 106,6%) (95,4%- 110,3%) (94,8%- 107,6%)

CmIn,ss 93,7%
(87,7% 100,2%)

96,6%
(88,2%- 105,7%)

96,4%
(88,2%- 105,4%)

Los intervalos de confianza de 90% de la relación de LSM derivada de los anÆlisisde los parÆmetrosfarmacocinØticos in-transformados AUCO-, Cmx,ss y Cmin,ss para todos los metabolitos de bupropion estuvieron entre 80,0-125,0%.

PAWC (Compuesto ponderado con actividad farmacologica)
Los parametros farmacocinØticos de los PAWC segün administraciones orales de un comprimido de Bupropion HBr XL 1 x 522 mg y comprimidos de Bupropion HBr XL 3 x 174 mg (dosis total de 522 mg) son los siguientes.

ParÆmetro PAWC
Comprimido de Bupropion
HBr XL 1 x 522 mg

Comprimidos de Bupropion
HBr XL 3 x 174 mg

Media geomØtrica (%CV)
AUCO- (nmolh!mL)
CmÆx,ss (nmol/mL)
CmIn,ss (nmol/mL)

82,2 (39,1%) 82,9 (32,4%)
4,64 (34,7%) 4,51 (27,0%)
2,73 (45,5%) 2,91 (39,3%)
TmÆx media (Mm
TmÆx,ss (h) 5,00 (2,00 7,00) 5,00 (3,00 12,00)
Media aritmØtica (– SD)
AUCO- (nmoFhlmL)
CmÆx,ss (nmol/mL)
Cmfn,ss (nmol/mL)
Cssprom (nmol/mL)
Fluctuación (%)
Oscilación (%)

87,4 27,8 86,5 23,6
4,88 1,45 4,65 1,12
2,96 1,09 3,09 1,03
3,64:h 1,16 3,61 0,983
55,2 18,6 46,3 16,9
73,8 38,4 57,0 26,2

Los intervalos de confianza de 90% no paramØtricos para el TmÆx,ss medio de la diferencia prueba - referencia (efecto de formulaciOn) fue [-1,50; -0,50] para PAWC.

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Los resultados farmacocinØticos para los conjuntos de datos de PAWC segün administraciones orales de un comprimido de Bupropion HBr XL 1 x 522 mg y comprimidos de Bupropion HBr XL 3 x 174 mg (dosis total de 522 mg) son los
siguientes.
Relacjones de LSM (Intervalos de confianza de 90%)
ParÆmetro PAWC
Comprimido de Bupropion HBr XL de Biovail 1 x 522
mg (A) vs.. Comprimidos de Bupropion HBr XL de
Biovail 3 x 174 mg (B)
AUCO-,r 99,1% (94,6% 103,8%)
Cmax,ss 102,9% (98,2% 107,7%)
CmIn,ss 94,2% (87,9% 100,9%)

Los intervalos de confianza de 90% de la relación de LSM derivada de los anªlisis de los parÆmetros farmacocinØticosin-transformados AUCO-, CmÆx,ssy CmIn,ss para PAWC estuvieron entre 80,0-125,0%.

Conclusion:

Tras repetidas administraciones por via oral de comprimidos de bromhidrato de bupropion XL (522 mg vs.. 3 x 174 mg) a voluntarios saludables, los intervalos de confianza de 90% de las relaciones de LSM derivadas de los anÆlisisde los parÆmetros farmacocinØticos In-transformados AUCO-, CmÆx,ssy Cmin,ss para bupropion, hidroxibupropion, treoamino alcohol de bupropion, eritroamino alcohol de bupropion y PAWC en plasma estuvieron entre 80,0-125,0%.

En conclusion, los resultados del estudio de proporcionalidad de concentraciOn de ía dosis actual demostraron que repetidas administraciones por via oral de comprimidos de bromhidrato de bupropion XL de Biovail como an comprimido itnico de 522 mg y tres comprimidos de 174 mg son equivalentes en condiciones de ayuno y en varias dosis.

Tabla: ParÆmetrosfarmacocinØticos medios (–SD) para Bupropion (n = 29)
1 x Comprimido de 3 x Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de522mg del74mg
(06M1 19P) (06M062P)
(n=29) (n=29)
AUC0t(ng*l1r/mL) 1730E494 TF63–174

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CmÆx (ng/mL) 176,1+63,6 166,9–53,0
CmIn (ng/mL) 31,4+13,4 31,3–13,2
Cprom (ng/mL) 72,1–20,6 73,5–23,9
TmÆx(hr)* 4,0 (2,0,7,0) 5,0 (3,0,6,1)

Grado de fluctuación
(%)

199,9–48,6 186,7–24,9

* Medio (rango)

Tabla: Resumen de estadIsticas para Bupropion (n = 29)

1 x Cornprimido de Bupropion HBr XL de 522 mg Versus 3 x Comprimidos de Bupropion HBr XL de 174 mg

Relación de medias Intervalo de confianza
geomØtricas geomØtrica de 90%
AUCO-’r 97,8% 91,4 104,5%
CmÆx 103,2% 96,0-111,0%
CmIn 99,0% 90,7 108,0%

5 Tabla: ParÆmetrosfarmacocinØticos medios (–SD) para Hidroxibupropion (n = 29)
1 x Comprimido de 3 x Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de522mg del74mg
(06M1 19P) (06M062P)
(n=29) (n’29)
AUCO-’r (ng*/mL) 27738–10583 27389–9385
CmÆx (ng/mL) 1457,0–530,3 1401,94445,8
CmIn (ng/mL) 985,9–414,8 1042,4–410,4
Cprom (ng/mL) 1155,7–441,0 1141,21391,0
TrnÆx (hr)* 5,0 (2,0, 8,0) 7,0 (3,0, 12,0)

Grado de fluctuaciOn

43,0–17,3 34,9–15,4 (%)
Relación metabolito/
15,7–6,8 16,0–8,3
original

* Medio (rango)

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Tabla: Resumen de estadisticas para Hidroxibupropion (n = 29)

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1 x Comprimido de Bupropion HBr XL de 522 mg Versus 3 x Comprimidos de Bupropion HBr XL de 174 mg

Relación de medias
geometricas

Intervalo de confianza
geomØtrica de 90%
AUCO-’r 99,5% - 95,3 - 104,0%
CmÆx 102,2% 98,0 106,6%
CmIn 93,7% 87,7 100,2%

Tabla: ParÆmetrosfarmacocinØticos medios (–SD) para treoamino alcohol de bupropion (n29)
1 x Comprimido de 3 x Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de522mg del74mg
(06M1 19P) (06M062P)
(n=29) (n29)
AUCO-t (ng*hr/mL) 14840–5929 14730–6138
CmÆx (ng/mL) 805,2–3008,7 784,9–310,9
Cmmn (ng/mL) 496,2–219,5 503,6–217,9
Cprorn (ng/mL) 618,4–247,1 613,8+255,8
TmÆx(hr)* 650 (2,0, 10,0) 7,0 (3,0, 14,0)
Grado de fluctuaciOn

51,2–19,0 46,7113,3 (%)
Relacjón metabolito!

857–2,7 8,512,8 original
* Medio (rango)

Tabla: Resumen de estadIsticas para treoamino alcohol de bupropion (n = 29)

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1 x Comprimido de Bupropion HBr XL de 522 mg Versus 3 x Comprimidos de Bupropion HBr XL de 174 mg

RelaciOn de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUCO-t 100,9% 94,2 108,1%
CmÆx 102,6% 95,4-110,3%
Cmiii 96,6% 88,2-105,7%

Tabla: ParÆmetros farmacocinØticosmedios (:LSD) para eritroamino alcohol de bupropion (n=29)
1 x Comprimido de 3 x Comprimidos de
Bupropion HBr XL Bupropion HBr XL
de522mg del74mg
(06M1 19P) (06M062P)
(n=29) (n29)
AUCOr(ng*hr/mL) 3048–1135 3006–1074
Cmax(ng/mL) 155,3–55,4 153,6–54,9
Cmfn(ng/mL) 111,3–46,5 111,6–40,8
Cprom (ng/mL) 127,0–47,3 125,3–44,8
TmÆx (hr)* 6,0 (2,0, 10,0) 8,0 (3,0, 16,0)

Grado de fluctuación
37,1–17,0 33,5–12,6
(%)
Relación metabolito!
1,8–0,6 1,8–0,6
original
* Medio(rango)

Tabla: Resumen de estadIsticas para eritroamino alcohol de bupropion (n = 29)

1 x Comprimido de Bupropion HBr XL de 522 mg
Versus 3 x Comprimidos de Bupropion HBr XL de
174 mg

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Re!ación de medias
geomØtricas

Intervalo de confianza
geomØtrica de 90%
AUC0-r 100,7% 94,6 107,2%
CmÆx 101,0% 94,8 107,6%
Crain 96,4% 88,2-105,4%

Tabla: ParÆmetrosfarmacocinØticos medios (::LSD) para PAWC (n = 29)
1 x Comprimido de 3 x Comprimidos de
Bupropion HBr XL Bupropion HBr XL
ParÆmetros

de522mg del74mg farmacocinØticos
(06M1 19P) (06M062P)
(n=29) (n=29)
AUCO-t

87,4–27,8 86,5–23,6 (nmol*jii/mL)
CmÆx(nmol/mL) 4,9–1,5 4,7–1,1
Cmin (nmol/mL) 3,0–1,1 3,1–1,0
Cprom (nmol/mL) 3,6–1,2 3,6–1,0
TmÆx(hr)* 5,0 (2,0, 7,0) 5,0 (3,0, 12,0)

Urado de fluctuaciOn

55,2+18,6 46,3–16,9 (%)
* Medio (rango)

Tabla: Resumen de estadIsticas para PAWC (n = 29)

1 x Comprimido de Bupropion HBr XL de 522 mg
Versus 3 x Comprimidos de Bupropion HBr XL de
174 mg

Relacjón de medias
geomØtricas

Intervalo de conflauza
geomØtrica de 90%
AUC0-r 99,1% 94,6 103,8%
CmÆx 102,9% 98,2 107,7%
CmIn 94,2% 87,9 100,9%

EJEMPLO 8:

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El anÆlisisde impureza de 3’-cioro-2-bromopropiofenona en muestras de Bupropion HBr
en este ejemplo se basa en la PRUEBA LfMITE DE 1-JPLC. El pico de impureza,
presente finalmente en el cromatograma de muestra, no deberIa exceder en area el pico
del analito en el cromatograma de "solución de referenda" correspondiente a una concentración de 3 ppm de impureza en la muestra. El mØtodo utiliza una columna Cl 8 con detección LTV a 255 nm y una fase móvil isocrÆtica.

Condiciones de funcionamiento
Instrumento: Bomba de HPLC Shimadzu LC- 1OAD,
controlador de sistema SCL- 1 OA,
autoinyector SIL- 1 OA (o equivalente)

Columna: fase: Waters XBridge C18
tamaæo departIcuia: 5 mm
longitud de columna: 250 mm
ID de columna: 4,6 mm
Volumen de inyección: 50 ml
Detector: Detector de UV Shimadzu modelo SPD-
1 OA (o equivalente)
Longitud de onda: UV, 255 imi
Fase móvil: ver preparación abajo
Columna T: 40°C
Flujo: 1,2 ml/min.

Fase móvil: mezclar 1100 ml de acetonitrilo y 1000 ml de soiución de Na2HPO4 20 mM en agua de HPLC. Ajustar ci pH a pH 7,2 con Æcido fosfOrico85%.

Solución de muestra: pesar exactamente 500 mg de muestra y transferirlos a un matraz volumØtrico de 50 ml. Disolver y diluir a volumen con agua de HPLC (10 mg/ml).

Solucjón de referencia (solución de cantidades conocidas de 3’-Cloro-2-bromopropiofenona 3 ppm): pesar exactamente 15 mg (– 1 mg) de 3 ’-Cloro-2-bromopropiofenona WSTD en un matraz volumØtrico de 100 ml. Disolver y diluir a volumen con acetonitrilo (0,15 mg/ml, sol.A). Colocar con una pipeta exactamente 1,0 ml de "soLA" en otro matraz volumdtrico de 100 ml y diluir a volumen con agua de HPLC (0,0015 mg/ml, sol. B). En un matraz volumØtrico de 50 ml pesar unos 500 mg de Bupropion.HBr WSTD y agregar exactamente 1,0 ml de "sol.B". Disolver y diluir a

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volumen con agua de HPLC (Bupropion.HBr 10 mg/ml y analito 0,03.ig/m1, que
corresponde a 0,0003% (3ppm) de la eoncentración de muestra 10,000 ig/m1).

Prueba de aptitud del sistema: acondicionar el sistema de HPLC con las "condiciones de funcionamiento" prescritas hasta obtener una Ilnea base estable, plana, y luego inyectar 50 ml de la "solución de referencia". Permitir que prosiga el anÆlisis.La prueba de aptitud del sistema cumple los requisitos si:
1) Especificidad y sensibilidad: El pico de 3’-Cloro-2-bromopropiofenona se determina a partir de Bupropion y otros picos de impureza finales y tiene un RT
de 13 mm. – 2 mm. El area pico del analito es NLT 5000.
2) Precision: el RSD% de todas las areas pico del analito obtenidas en los cromatogramas de ía "solución de referencia" es NMA 20%.

Procedimiento: al cumplirse la aptitud del sistema inyectar separadamente 50.il de soluciones de referencia y de muestra. Registrar los cromatogramas y medir las respuestas de area pico de los picos de impureza de 3’-Cloro-2-bromopropiofenona.

Evaluación:

ldentificación: identificar ía impureza de 3 ’-Cloro-2-bromopropiofenona en los cicios de muestra, de existir, mediante la comparación de los RT pico con los ciclos de ía "solución de referencia". El RT esperado es el siguiente:

TABULACION RT/ RRT
Compuesto RT mm.
3’-Cloro-2-bromopropiofenona 13 mm. 2 mm

Evaivación ifmite: cualquier pico finalmente presente en el cromatograma de muestra identificado como 3’ -Cloro-2-bromopropiofenona deberfa tener un area pico NMA el area de pico media de la 3’-Cloro-2-bromopropiofenona en los duplicados de la "solución de referencia" correspondientes a un contenido de impureza de 3 ppm (0,0003%) en ía muestra. Para el informe de resultado considerar la siguiente tabulación: TABULACION DE INFORME DE RESULTADO
Impureza Informe

el drea pico de la 3’-Cloro-2- <3 ppm
bromopropiofenona es inferior at area de
referencia de 3 ppm
el area pico de la 3’-Cloro-2- > 3 ppm
bromopropiofenona es superior al area de

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referencia de 3 ppm

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SENSIBILIDAD DEL METODO

Impureza LOQ LOD 3’-Cloro-2-

bromopropiofenona

no aplicable a prueba lImite 1 ppm*
(0,01.tgIm1)
* 1 ppm 0 0,0001% en cuanto a la concentraciOn de la muestra 10,000 g/m1.

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Resultados:

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Este ejemplo describe un mØtodo de HPLC/UV especificamente para detectar la impureza de 3 ’-Cloro-2-bromopropiofenona. Para aumentar la sensibilidad, la longitud de onda UV del detector se fijó en la absorciOn maxima para el analito que corresponde a 255 nm, y la fase móvil se ajustO para afilar el pico del analito lo mÆsposible. Las condiciones de funcionamiento del mØtodo como una "PRUEBA LfMITE de 3 ppm" se informan aqul. Se analizaron los lotes tabulados de API. Los resultados muestran que 3’- Cloro-2-bromopropiofenona estÆmuy por debajo del ilmite de detección prÆcticade 1 ppm en cada lote analizado.

RESULTADOS DEL AINALISIS DE LOTE
PRUEBA LIMITE DE 3 PPM PARA 3’-CLORO-2-BROMOPROPIOFENONA EN BROMIEJIDRATO DE BUPROPION
LOTE RESULTADO
D00894 NO DETECTABLE
D00895 NO DETECTABLE
D00896 NO DETECTABLE
06PK0970 NO DETECTABLE
06PK0971 NO DETECTABLE
LtMITE DE DETECCION: 1 ppm

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Tabla 1 Contenidos y cantidades de cada ensayo de cada material por parte
Materiales Cantidad (g)
Parte 1 Parte 2 Parte 3 Parte 4 Parte 5
Bupropion HBr 2062,5 2062,5 2062,5 2062,5 2062,5
PVA 68,75 68,75 68,75 68,75 68,75
Agua 1452,5 1452,5 1452,5 1452,5 1452,5
purificada

5 Tabla 2 Resumen de las especificaciones para el procedimiento de granulacion.
Especificación Jntervalo Referencia
Velocidad del ventilador Lenta Lenta
Volumen de aire (CMI-1) 60-65 65
Temperatura de salida (°C) 35-45 40
Temperatura de alimentaciOn (°C) 60-65 65
Temperatura del producto (°C) 35-55 45
Presión del aire de pulverizaciOn 35 35
(Bar/psi)
Velocidad de bomba (rpm) 18 18
Velocidad de flujo del lfquido 13 13
(g/min)
Punto de rocIo del lecho 0 0
(MMWC)
Punto de roclo del filtro 100-300 200
(MMWC)

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Tabla 3 La cantidad de lubricante en la formulación final fue de 343,75 g, lo que constituyó 3,125% del total.
Materiales Cantidad (g)
Parte 1 2131,25
Parte2 2131,25
Parte3 2131,25
Parte4 2131,25
Parte5 2131,25
COMPRITOLfi 888 343,75
Total 11000,0

Tabla 4 Resumen de especificaciones para el ajuste de la compresora de comprimidos.

. 5.ParÆmetros Ajuste/intervalos
Espesor antes de comprimir (mm) 2
Espesor de control (mm) 1,5
Espesor de llenado (mm) 7-8
Presión de sobrecarga (ton) 1,5-2,0
Comprimidos por minuto 450-500
Velocidad del alimentador 1-2
Control del alimentador Auto

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labia 5 Resumen de las especificaciones para la compresión
ParÆmetros Especificación para Especificación para
comprimido de 174 comprimido de 348 mg
mg

Peso de cada comprimido (mg) 185,615% 371,21 5%
(176,3 mg-194,9 mg) (352,6 mg-389,8 mg)
Peso promedio de los 185,6 3% 371,2:L 3%
comprimidos (mg) (180,0 mg-191,2 mg) (360,1 mg-382,3 mg)
Dureza del comprimido (SC) 6,0-12,0 6,0-12,0
Espesor del comprimido (mm) 5,0-6,0 4,5-5,0
Friabilidad (%) <0,8 <0,8

labia 6: Formulaciones usadas como el recubrimiento de etilcelulosa (por ejemplo,
5 ETHOCELfi o EC) en los nücleos de bupropion HBr de 174 mg y 348 mg. FORMULACION 1 FORMULACION 2 FORMULACION 3
ETHOCELfi ETHOCELfi ETHOCELfi
(Etilcelulosa) (Etilcelulosa) (Etilcelulosa)
Estandar 100 Premium EstÆndar100 Premium Estªndar 100 Premium
Povidona USP Povidona USP Povidona USP

(KOLLIDONfi 90F) (KOLLIDONfi 90F) (KOLLIDONfi 90F)
Polietilenglicol 4000 Polietilenglicol 4000 Polietilenglicol 4000
Alcohol etfljco 95% USP Sebacato de dibutilo Alcohol etIlico 95% USP
Alcohol isopropilico (AlP) Alcohol etilico 95% USP

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Tabla 7: Formulaciones usadas como los recubrimientos finales en los comprimidos de bupropion HBr de 174 mg y 348 mg.
FORMULACION A FORMULACION B
EUDRAGITfi L30D-55 EUDRAGITfi L30D-55
Chroma-Tone DEB 5156-CLE SYLOIDfi 244FP

Agua purificada Polietilenglicol 4000
Citrato de trietilo
Agua purificada

5 Tabla 8: Resumen de especificaciones que se mantuvieron constantes en el proceso de recubrimiento con etilcelulosa.
ParÆmetrosdel proceso Intervalos de Referenda
operaciOn
Temperatura de entrada para SV: 401 5 40
recubrimiento (°C) PV: 40 5
Temperatura de entrada para secado 30-35 35
(°C)
Temperatura de salida 30 10 30
Temperatura del produeto 25-35 28
Presión diferenejal AP (W.C) (-0,1)-(-0,12) -0,10
Flujo de suministro de aire (CFM) 200 50 200
Velocidad de la paila (rpm) 2,5-12 5,0
Aire de pulverizaciOn (psi) 35-40 35
Aire patron (psi) 20-30 25
Velocidad de pulverización (g/min) 5-15 60

Tabla 9: Resumen de especificaciones que se mantuvieron constantes en el proceso de
10 recubrimiento final.
ParÆrnetrosdel proceso Intervalos de Referencia
operaciOn
Temperatura de entrada para SV: 50 – 5 50
recubrimiento (°C) PV: 50 – 5
Temperatura de entrada para 40 – 5 40
secado (°C)

332

LI

11

[ii

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Temperatura de salida 35 5 38
Temperatura del producto. 35 2 35
Presión diferencial AP (W.C) (-0,1)-(-0,12) -0,10
Flujo de suministro de aire (CFM) 200 50 200
Velocidad de lapaila (rpm) 2,5-15 12,0
Aire de pulverizaeión (psi) 25-35 35
Aire patron (psi) 20-30 25
Velocidad de pulverización 5-15 13,0
(g/min)

Tabla 10: Materiales usados en una parte del late, porcentaje de cada componente, cantidad por comprimido y cantidad por lote, para BUP-HBr-XL-009-5
Materiales Cantidad en el lote
mg/comprimido (g)
Bupropion HBr 93,75 348,00 1993,75
PVA 3,125 11,60 68,75
COMPRITOLfi 888 3,125 11,60 68,75
Total 100,00 371,2 mg 2131,25

Tabla 11: Resultados obtenidos usando punzones de 9mm para el lote BUP-HBr-XL-009-5.
ParÆmetros Teórico Real

Peso promedio de los 371,2 mg 371,5 mg
comprimidos
Dureza promedio 6,0-12,0 SC 10,77 SC
Espesor promedio 5,0-6,0 mm 5,60 mm
Friabilidad 0,8% 0%

Tabla 12: Resultados obtenidos usando punzones de 10 mm para el lote BUP-HBr-XL-1II51

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ParÆmetros Teórico Real

Peso promedio de los 371,2 mg 366,5 mg
comprimidos
Dureza promedio 6,0-12,0 SC 7,50 SC

5 Espesor promedio 5,0-6,0 mm 4,97 mm
Friabilidad <0,8% 0%

Tabla 13: Materiales usados en una parte del lote, porcentaje de cada componente, cantidad por comprimido y cantidad par lote, para el late BUP-HBr-XL-021-5
Materiales Cantidad en el lote
mg/comprimido (g)
Bupropion HBr 93,75 174,00 1993,75
PVA 3,125 5,80 68,75
COMPRITOLfi 888 3,125 5,80 68,75
Total 100,00 185,60 2131,25

Tabla 14: Resultados obtenidos usando punzones de 7 mm para el lote BUP-HBr-XL-

02 1-5.
ParÆmetros Teórico Real

Peso promedio de los 185,6 mg 186,8 mg
comprimidos
Dureza promedio 6,0-12,0 SC 9,23 SC
Espesor promedio 4,5-5,0mm 4,70mm
Friabilidad <0,8% 0%

15 Tabla 15: Materiales usados en el recubrimiento de etilcelulosa sus cantidades para el
lote BUP-HBr-XL-348-0 1 3-5.
Materiales Cantidad de
Contribución en el lote sOlidos en
al total de la (g) soluciOn
solución

ETHOCELfi (etilcelulosa) estÆndar100 Premium 3,60 77,44 38,74
Povidona USP (KOLLIDONfi 90F) 4,600 99,22 49,64
PEG 4000 1,07 23,23 11,62
Alcohol etIlico 95% USP 86,44 1859,50 N/A

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Alcohol isopropIlico 99% USP 4,54 97,87 N/A
Total 100,00 2151,00 100,00
El componente sólido total de la formulación incluyO 77,44 g de etilcelulosa (por ejemplo, ETHOCELfi), 99,22 g de Povidona y 23,23 g de PEG 4000, que dio una cantidad sólida total de 199,89g. El componente sólido de la fonnuiación constituyó el 9% de la solución total y el 91% restante estuvo constituido de lIquido.

Tabla 16: Pesos teOricos y reales de los comprimidos con 28 mg, 30 mg, 32 mg y 34 mg de aumento de peso para el lote BUP-HBr-XL-348-013-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
28,0 400,0 401,3
30,0 402,0 402,6
32,0 404,0 404,5
34,0 406,0 406,8

10 Tabla 17: Materiales usados en el recubrimiento final y sus eantidades para ci lote BUP-
HBr-XL-348-0 13-5.
Materiales % Cantidad en Cantidad % de
Contribución el lote de sólido sólidos

al total de la (g) (g) en
solución solución
EUDRAGITfi L30 D-55 22,73 104,8 31,44 65,00
Chroma-Tone DEB 5156-CLE 3,66 16,90 16,90 35,00
Aguapurificada(1) 21,78 100,40 N/A N/A
Aguapurificada(2) 51,89 239,20 N/A N/A
Total 100,00 460,95 48,34 100,00
El porcentaje de EUDRAGITfi, sólido, que contribuyó a la cantidad total de sólidos fue
de 65%.

El porcentaje de Chroma-Tone, sólido, que contribuyO a la cantidad total de sOlidos fue
15 de 35%.

La cantidad total de sólidos (48,34g) fue de 10,5% del total de la solución.

Tabla 18; Pesos teóricos y reales de los comprimidos con 4 mg, 5 mg, 6 mg y 7 mg de
20 aumento de peso.

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Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)

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4,0 410,0 410,5
5,0 411,0 410,8
6,0 412,0 412,4
7,0 413,0 413,9

Tabla 19: Materiales usados en el recubrimiento de etilcelulosa y sus cantidades para el lote BUP-HBr-XL-348 mg-018-5.
Materiales % Cantidad % de
Contribución en el sólidos en

al total de la lote (g) solución

solución

ETHOCELfi (etilcelulosa) estÆndar 100Premium 3,42 73,57 38,00
Povidona USP (KOLLIDONfi 90F) 4,41 94,86 49,00
PEG 4000 1,17 25,17 13,00
Alcohol etIlico 95% USP 86,45 1859,53 N/A
Alcohol isopropIlico 99% USP 4,55 97,87 N/A
Total 100,00 2151,00 100,00
5 El total de sólidos incluyó 73,57 g de etilcelulosa, 94,86 g de povidona y 25,17 g de PEG 4000. Esto dio una cantidad de sólidos totales de 193,6 g.

Tabla 20: Pesos teOricos y reales de los comprimidos con 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso para el lote BUP-HBr-XL-348 mg-018-5.
Aumento de peso Peso teOrico (mg) Peso real (mg)
(mg)
2630 398,0 397,7
28,0 400,0 399,5
30,0 402,0 401,5
32,0 404,0 404,0

10

Tabla 21: Materiales usados en el recubrimiento final y sus cantidades para el lote BUP-HBr-XL-348 mg-018-5.
Materiales % Contribucion Cantidad en el Cantidad de % de

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al total de la lote sólido sólidos en

solución (g) (g) solución
EUDRAGITfi L30D D-55 22,75 104,86 31,46 65,00
SYLOIDfi 244FP 2,62 12,08 12,08 25,00
CARBOWAXfi 4000 0,70 3,22 3,22 6,65
Citratodetrietilo 0,36 1,64 1,64 3,39
Agua purificada (1) 33,84 156,00 N/A N/A
Aguapurificada(2) 39,73 183,15 N/A N/A
Total 100,00 460,95 48,40 100,00
El porcentaje de EUDRAGITfi, sólido, que contribuyO a la cantidad total de sOlidos fue de 65%.

Los porcentajes de SYLOIDfi, CARBOWAXfi 4000 y citrato de trietilo que
contribuyeron a la cantidad total de sólidos fueron de 25%, 6,65% y 3,39%,
5 respectivamente. Esto dio un total de 35%.
La cantidad total de sólidos (48,4 g) fue de 10,5% del total de la solución.

 10

Tabla 22: Pesos teóricos y reales de los comprimidos con 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso para el lote BUP-HBr-XL-348 mg-018-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
4,0 408,0 408,5
5,0 409,0 409,3
6,0 410,0 410,7
7,0 411,0 411,1

Tabla 23: Materiales usados en el recubrimiento de etilcelulosa y sus cantidades para el lote BUP-HBr-XL-174 mg-022-5.
Materiales % Cantidad % de
Contribución en ci lote sóiidos en

al total de la (g) solución
solución

ETI-IOCELfi (etilcelulosa) estÆndar100 3,60 116,12 40,00

Premium

PovidonaUSP (KOLLIDONfi 90F) 4,32 139,34 48,00
PEG 4000 1,08 34,84 12,00

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Alcohol etIlico 95% USP 86,45 2788,54 N/A
Alcohol isopropilico 99% USP 4,55 146,76 N/A
Total 100,00 3225,60 100,00
El total de sóiidos incluyó 116,12g de ETHOCELfi, 139,34g de povidona y 34,84g de
PEG 4000. Esto dio una cantidad total de sólidos de 290,3g.

Tabla 24: Pesos teóricos y reales de los comprimidos con 20 mg, 22 mg, 24 mg, 26 mg,
5 28 mg, 29 mg y 30 mg de aumento de peso para ci lote BUP-HBr-XL-174 mg-022-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
20,0 206,0 206,1
22,0 208,0 207,8
24,0 210,0 210,2
26,0 212,0 211,5
28,0 214,0 213,7
29,0 215,0 214,9
30,0 216,0 216,5

Tabla 25: Materiales usados en ci recubrimiento final y sus cantidades para ci lote BUP-HBr-XL- 174 mg-022-5.
Materiales % Cantidad Cantidad de % de
Contribución en el lote sólido sOiidos en
al total de la (g) (g) solución

solución

EUDRAGITfi L30D D-55 22,75 104,86 31,46 65,0
SYLOIDfi 244FP 2,62 12,08 12,08 25,0
CARBOWAXfi 4000 0,70 3,22 3,22 6,65
Citrato de trietilo 0,36 1,64 1,64 3,39
Agua purificada (1) 33,84 156,00 N/A N/A
Agua purificada (2) 39,73 183,15 N/A N/A
Total 100,00 460,95 48,40 100,00
10 El porcentaje de EUDRAGITfi, sóiido, que contribuyó a la cantidad total de sóiidos fue
de 65%.

Los porcentajes de SYLOIDfi, CARBOWAXfi 4000 y citrato de trietilo que contribuyeron a la cantidad total de sólidos fueron de 25%, 6,65% y 3,39%, respectivamente. Esto dio un total de 35%.
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La cantidad total de sólidos (48,4 g) fue de 10,5% del total de la solución.

Tabla 26: Pesos teóricos y reales de los comprimidos con 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso para el lote BUP-HBr-XL-174 mg-022-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
4,0 219,0 219,4
5,0 220,0 220,2
6,0 221,0 221,2
7,0 222,0 223,0
5

Tabla 27: Materiales usados en el recubrimiento de etilcelulosa sus cantidades para el
lote J3UP-HBr-XL348 mg-023-5.
Materiales Cantidad de
Contribución en el lote sólidos en

al total de la (g) solución
solución
ETHOCELfi (etilcelulosa) estÆndar 100 3,69 79,37 42,71
Premium

Povidona USP (KOLLIDONfi 90F) 3,69 79,37 42,71
PEG 4000 1,26 27,11 14,58
Sebacato de dibutilo, NF 0,36 7,75 N/A
Alcohol etIlico 95% USP 91,00 1957,4 N/A
Total 100,00 2151,00 100,00
El total de sOlidos incluye 79,37 g de ETHOCELfi, 79,37 g de povidona 27,11 g de
PEG 4000 7,75 g de sebacato de dibutilo. Esto dio una cantidad total de sólidos de
10 193,6g.

Tabla 28: Pesos teOricos y reales de los comprimidos con 26 mg, 28 mg, 30 mg y 32 mg
de aumento de peso para el lote BUP-HBr-XL-348 mg-023-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
26,0 398,0 399,3
28,0 400,0 401,0
30,0 402,0 401,7
32,0 404,0 402,7

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Tabla 29: Materiales usados en el recubrimiento de etilcelulosa y sus cantidades para el lote BUP-HBr-XL-348 mg-025-5.
Materiales Cantidad de
Contribución en ci lote sOlidos en

al total de la (g) solución
solución

ETHOCELfi (etilcelulosa) estªndar 100 3,69 79,40 41,00
Premium

Povidona USP (KOLLIDONfi 90F) 3,78 81,30 42,00
PEG 4000 1,53 32,90 17,00
Alcohol etilico 95% USP 91,00 1957,40 N/A
Total 100,00 2151,00 100,00
*E1 total de sólidos inciuyó 79,40g de ETHOCELfi, 81,30 g de povidona y 32,90 g de
5 PEG 4000. Esto dio una cantidad total de sólidos de 193,6 g.

10

Tabla 30: Pesos teóricos y reales de los comprimidos con 26 mg, 28 mg, 30 mg y 32 mg
de aumento de peso para el lote BUP-HBr-XL-348 mg-025-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
26,0 398,0 397,8
28,0 400,0 400,6
30,0 402,0 401,4
32,0 404,0 402,2

Tabla 31: Materiales usados en ci recubrimiento final y sus cantidades para ci lote BUP HBr-XL-348 mg-025-5.
Materiales % Cantidad en Cantidad de % de
ContribuciOn el lote (g) sóiido sólidosen
al total de la (g) solución

soiución

EUDRAGITfi L30D D-55 19,77 91,13 27,34 56,50
SYLOIDfi 244FP 3,15 14,52 14,52 30,00
CARBOWAXfi 4000 0,95 4,36 4,36 9,00
Citratodetrjetiio 0,47 2,17 2,17 4,50

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Agua purificada (1) 21,70 100,00 N/A N/A
Agua purificada (2) 53,96 248,77 N/A N/A
Total 100,00 460,95 48,39 100,00
El porcentaje deEUDRAGITfi, sólido, que contribuyó a la cantidad total de sólidos fue

de 65%.

Los porcentajes de SYLOIDfi, CARBOWAXfi 4000 y citrato de trietilo que contribuyeron a la cantidad total de sólidos fueron de 30%, 9% y 4,5%, respectivamente.
5 Esto dio un total de 43,5%.
La cantidad total de sólidos (48,39 g) fue de 10,5% del total de la solución.

Tabla 32: Pesos teóricos y reales de los comprimidos con 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso para el lote BUP-HBr-XL-348 mg-025-5.
Aumento de peso Peso teórico (mg) Peso real (mg)

4,0 408,0 408,3
5,0 409,0 408,8
6,0 410,0 409,5
7,0 411,0 411,1

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Tabla 33: Materiales usados en el recubrimiento de etilcelulosa sus cantidades para el
lote BUP-HBr-XL-348 mg-026-5.
Materiales Cantidad de
Contribución en el lote sólidos en

al total de la (g) soluciOn

solución

ETHOCELfi (etilcelulosa) estÆndar100 3,69 79,37 41,00
Premium

Povidona USP (KOLLIDONfi 90F) 3,69 79,37 41,00
PEG 4000 0,36 7,75 4,00
Sebacato de dibutilo, NF 1,26 27,11 14,00
Alcohol etIlico 95% USP 91,00 1957,4 N/A
Total 100,00 2151,00 100,00
El total de sólidos incluyo 79,37 g de ETHOCELfi, 79,37 g de povidona 7,75 g de PEG
15 4000 27,11 g de sebacato de dibutilo. Esto dio una cantidad total de sOlidos de 193,6 g.

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Tabla 34: Pesos teóricos y reales de los comprirnidos con 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso para el lote BUP-HBr-XL-348 mg-026-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
26,0 398,0 398,8
28,0 400,0 400,5
30,0 402,0 402,5
32,0 404,0 403,6

5 labia 35: Materiales usados en el recubrimiento de etilcelulosa y sus cantidades para ci
lote BUP-HBr-XL-174 mg-027-5.

41 Materiales % Cantidad % de

Contribución en el lote sOlidos en

al total de la (g) solución
soluciOn

ETHOCELfi (etilcelulosa) estÆndar 100 3,69 138,87 41,00

Premium

Povidona USP (KOLLIDONfi 90F) 3,78 142,25 42,00
PEG 4000 1,53 57,58 17,00
Alcohol etulico 95% USP 91,00 3424,63 N/A
Total 100,00 3763,33 100,00
El total de sólidos incluyó 138,87g de ETHOCELfi, 142,25 g de povidona y 57,58 g de PEG 4000. Esto dio una cantidad total de sólidos de 338,7 g.

10 Tabla 36: Pesos teóricos y reales de los comprimidos con 22 mg, 24 mg y 26 mg de
aumento de peso para el lote BUP-HBr-XL-174 mg-027-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
22,0 208,0 207,7
24,0 210,0 210,8
26,0 212,0 212,4

Tabla 37: Materiales usados en ci recubrimiento final y sus cantidades para ci lote BUP-HBr-XL- 174 mg-027-5.
Materiales % Cantidad Cantidad % de

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Contribución en el lote de sólido sólidos

al total de la (g) (g) en
solución solución
EUDRAGITfi L30D D-55 19,77 182,27 54,68 56,5
SYLOIDfi 244FP 3,15 29,03 29,03 30,0
CARBOWAXfi 4000 0,95 8,71 8,71 9,0
Citrato de trietilo 0,47 4,35 4,35 4,5
Agua purificada (1) 21,70 200,00 N/A N/A
Agua purificada (2) 53,98 497,26 N/A N/A
Total 100,00 921,62 96,77 100,00
El porcentaje de EUDRAGITfi, sólido, que contribuyO a la cantidad total de sólidos fue de 56,5%.
Los porcentajes de SYLOIDE, CARBOWAXfi 4000 citrato de trietilo que
contribuyeron a la cantidad total de sólidos fueron de 30,0%, 9,0% 4,5%,
5 respeetivamente.
Esto dio un total de 43,5%.
La cantidad total de sólidos (9,77 g) fue de 10,5% del total de la solución.

labia 38: Pesos teóricos y reales de los comprimidos con 4 mg, 5 mg, 6 mg y 7 mg de
10 aumento de peso para el tote BUP-HBr-XL-174 mg-027-5.
Aumento de peso Peso teórico (mg) Peso real (mg)
(mg)
4,0 216,0 216,6
5,0 217,0 217,6
6,0 218,0 217,8
7,0 219,0 219,8

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EFECTOS DEL CLORI-IIDRATO DE BUPROPION
EN EL MON ITOREO DE TRAZAS DE EEG EN LA
RATA

(10 RATAS FOR GRUPO)

TRATPMIENTO NUMERO TIEMPO OBSERVAC ONES

(mg/kg) DE RATA COMPORTAMIENTO ANAUSIS EEG ------------------------------

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hipo htpocampo
Actividad de crisis oonvuFsr9a breve haste 4 seguridos
Activsiad de crisis convulsive prolongada entre 4 y 60 segundos
T-1 a TO rag isti-o de hriea base (1 hora antes de la iriyeccion)
TO a T2 regustro unmediatamente despues de ta inyeccuon por 2 horse
sugno ausencia de sintomas
sugno + presenaa de sintomas

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Tabla 39(2)

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EFECTOS DEL CLORH1DRATO DE BUPROPION
EN EL MONITOREO DE TRAZAS DE EEG EN LA
RATA

(10 RATAS POR GRUPO)

TRATPMIENTO NUMERO TIEMPO OBSERVAC1ONES
(rn/kg) LiE RATA
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hipo hipocampo
Actividad de cnse convulsiva breve hasta 4 segundos
Actividad de crias convulawa prolongada entre 4 y 60 aeguridos
T-1 a TO registro de linea base (1 hora antes de la inyeccion)
TO a T2: registro inmedatamer,te despus de la inyecdós par2 hares.
slgrio ausenciadesinlomas
sgno 4- p,asenc4s de sintornas

EFECTOS DEL CLORJ-IIDRATO DE BUPROPION
EN EL MONJTOREO DE TRAZAS DE EEG EN LA
RATA

(10 RATAS POR GRUPO)

TRATAMENTO NUMERC TIEMPO I OBSERVACIONES

(mg/kg) DE RATA COMPORTAMIENTO ANALISIS EEG

MW

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EFECTOS DEL BRCMHIDRATO DE BUPROPION
EN EL MON(TOREO DE TRAZAS DE EEG EN LA
RATA

(10 RATAS POR GRUPO)

- TFATMIENTO NUMERO f TJEMPO OB$ERVACICNES

(mglkg) DE RATA jC0MPORTADiIENTO ANAUSIS EEG liD.
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AchY Wad la crisis convuIsNa prolongada eritre 4 y 60 se2undos
T-1 a TO registro de liea base (1 hors aches de la lnecxor)
TO a 12: reisrc in med iahamente despuds de la inyecoiôri por 2 horas.
sigro ausencia de suntomas

signo + presencua de sintomas * No se estaba re9istrando el sintonia (cloruo facuat durante la con exion)

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Tabla 40(2)

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LU IniOUOflOIn4 A ---4-...-.-..-
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Tabla 40(3)

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EFECTOS DEL BROMHIDRATO DE BUPROPON C
EN EL MONITOREO DE TRAZAS DE EEG EN LA
RATA

(IORATASPORGRUPO)

TRATAMIENTO NUMERO, TIEMPO - OBSERVACNES -
(mg(kg) DE RATA COMPORTPMIENTO ANALISIS EEC

Ag

I zo

II Il s t5

U Hi E U H
2 N N N N N N N
- C) O () 0 0 0 0

- 2-------------------------------------

TOT24L: E

- k-

QO33 r a

- 2 f -

TO _ - -
IC aT2 - - - -

OO6

T-1aTO i - - - - - - -’’ . TV a T2 BROMHIDRATO -

DE BIJPROPION I I a TO

100 TOaT2-- - - ItaTO

TtaT2 -A - -- -- - -1 C-----

711 TO i i - I --’ - - ------------------------------ ’- -

TOaT2 I -

; t:

TA a T I D -

so

::iii1

T0aT4 - 1i - cz carteza

hpo hipocampo
Actwdad de crisis convulsive breve hasta 4 segundos t1
Actwidad de crisis convulsiva protongada entre 4 y 60 seguridos
T-1 a TO registro de hnea base (1 hors antes de la inyeccrort)
TO a 12 registro inrnethatamente despises de la inyecoon por 2 horas
sigma ausencia de sintomas 00
slgrlo + presencla de sirtorrias
ON
Li-)

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Tabla 41

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EFECTOS DEL CLORHIDRATO DE BLJPROPICDN Y BROMHIDRATO DE BUPROPION EN EL MONITOREO DE TRAZAS DE EEC EN LA RATA

(10 RATAS POR GF?UPO)

Activ:dad do crisis convulsiva pro/ongags

DURACION DE LA CRISIS CONVULSIVA TRATAMIENTO CANTIDAD INICIAL
(mg/kg) DE
i.p. ANIMALES CORTEZA HIPOCAMPO
CON

media s.e.m. media sMm. ACTDAO

DE CRISIS

Clorhidrato de
bupropion 10 33 3 25 4
100

Bromhidrato

de bupropion 4 31 6 23 2

100

Prueba de [p JI al cuadrado * p e 0,05.

No de muertos (1/10)
NB: Las dosis do clorhidrato do bupropion (HCI) so expresan on mg/kg do sal y [as dosis do bromhidrato de bupropion (Her) se expresan an mg/kg de equivalente molar de HCI (factor dE correcciôn = 1,16).

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Tabla 42(1)

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EFECTOS DEL CLORHIDRATO DE BUPROPION Y BROMHIDRATO DE BUPROPION EN EL MONITQREO DE 7RAZAS DE EEG EN LA RATA

(10 RA TAS POR GRUPO)
Activklad de crisis convu/s va)J2a9Wi

BUPROPIQWl (100 mil

CRISIS CONVULSIVAS ELECTRICAS NUMERO DE ESTRUCTURA
RATA CEREBRALInicio Final Duraciófl

Q0336 Corteza .02:26.1 02:54.3 00:28.2
Hipocampo 02:216,8 02:51.7
00337 Cortaza .0:51.9 01.31.4

Hipocampo 00.5.8 01:2?i.7 QQ:1.9

Corteza 00:22.9 .030.4
Hipocampo 06:232

Q338 Corteza 01:17.0 01:48.1 60:311
Hipocampo 01:26:0 04:40.8
00.342 Corteza :3.53 0910.2 60:34.9

Hipocampo :06:36.3 08.,40.4 00044

Corteza

Hipocampo .06:423 09:10.2

00343 Corteza .06:06.0 001.4.0 00:14.8
Hipocampo 00:00.0 M12,6 00:12.6

Corteza 02:3:4.5 02:50.8
Hipocampo 02.36.0 62:50.6
Corteza 04.01.5
Hipocampo 04:02 0413.5
Corteza .916.5 08:216
Hipocampo .0612.0 w:21.8

344 Corteza 03:27 04:16.9 OO:49
Hipocampo .03.30.5 04:12.2 OC4 1.8
Corteza 00:3.2 05:55.7
Hipocampo

00346 Corteza 03:35.1 0411.8 00:365

Hipocampo 03:351 .0411.8 00:6.4

Corteza 08:38.1 68:59.0

Hipocampo :08:59.8 .09:00,8
Q034/3 Corteza 02:58.0 03::3.2
Hipocampo .02:599 03:30,5 003015
.00349 Corteza .04:03.8 04:37,0 00:332
Hipocampo 04:06:1 04:35,1 00:28.4
00351 Corteza 01:292 01:56.0 00:26.8
Hipocampo 01:39.4 0.1:55,6 00:15,4.
1,LMedia 00:32.9 00:24.8

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Tabla 42(2)

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EFECTOS DEL CLORHIDRATO DE BUPROPION Y BROMHIDRATO DE BUPROPION EN EL. MONITOREO DE TRAZAS DE EEG EN LA RATA

(10 RATAS POR GRUPO)
Act&tdad de cri.is conviilsiva po(onwd

BUPROPION HBr (100 mg/kg)

CRISIS CONVULSIVAS ELECTRICAS
NOMERO DE ESTRUCTIJRA

RATA CEREBRAL lnicio Final Duración

00352 Corteza 0t4?.7 02:04.8 00:16.9
Hipocampo 01:48.1 02:04,8 00:187

00353 Corteza 00:1.0 00:53.7 00:38.8

Hipocampo 00:24. 00:48.8 00:25,8

00354 Corteza 01:47.5 02:14.1 00:25.5
Hipocampo 01-49.0 02:14.6 00:24.7

00360 Corteza 04:11.4 04:55.8 00:42.3
Hipocampo 0414.2 04:39.5 00:25,3

Media 1 00:31.1 00:22.6

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RETVINDICACIONES

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1. Una composiciOn que comprende bromhidrato de bupropion y al menos un excipiente farmacØuticamente aceptable;
en donde la administración de una cantidad de un bromhidrato de bupropion a una primera rata resulta en menos incidencias de crisis convulsivas inducidas por bupropion y/o crisis convulsivas inducidas por bupropion menos graves en comparaciOn con las incidencias y/o gravedad de las crisis convulsivas inducidas por bupropion que resultan de la administración de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata; y
en donde las incidencias y/o la gravedad de las crisis convulsivas inducidas por bupropion se miden mediante un anÆlisisde electroencefalograma utilizando un electrodo profundo implantado en el hipocampo.

2. La composición de la reivindicación 1, que se encuentra en forma de comprimido.

3. La composiciOn de la reivindicaciOn 1, que es una formulación de liberaciOn modificada.

4. La composición de la reivindicación 1, que se encuentra en forma de comprimido y en donde ci bromhidrato de bupropion se encuentra dentro de un nücieo del comprimido, que comprende ademÆsun recubrimiento sobre el nücleo*

5. La composiciOn de la reivindicación 4, en donde ci recubrimiento es un recubrimiento de liberación controlada.

6. Una composicion que comprende bromhidrato de bupropion y al menos un excipiente faxmacØuticamente aceptable;
en donde la administración de aproximadamente 100 mg/kg de un bromhidrato de bupropion a una primera rata resulta en menos incidencias y/o gravedad de crisis convulsivas inducidas por bupropion en comparación con las incidencias y/o gravedad de crisis convulsivas inducidas por bupropion que resultan de la administración de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata; y

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en donde las incidencias y/o la gravedad de las crisis convulsivas inducidas por bupropion se
miden rnediante tin anÆlisisde electroencefalograma utilizarido un electrodo profundo
implantado en el hipocampo.

7. Un mØtodo para tratar un sujeto con riesgo de padecer crisis convulsivas inducidas por
bupropion que necesita un tratarniento con bupropion, comprendiendo el mØtodo:
administrar una composición que comprende bromhidrato de bupropion a dicho sujeto en una cantidad suficiente para tratar dicho sujeto.

8. El mØtodo de la reivindicación 7, en donde la composición comprende una cantidad de bromhidrato de bupropion que se selecciona de 174 mg, 348 mg y 522 mg.

9. El mØtodo de la reivindicaciOn 7, en donde la composición se encuentra en forma de comprimido y la administración comprende la administraciOn oral.

10, El mØtodo de la reivindicación 7, en donde la composición es una fonnulación de liberaciOn modificada.

ii. La composición de la reivindicación 7, en donde la composición se encuentra en forma de comprimido y en donde el bromhidrato de bupropion se encuentra dentro de un rncleo del comprimido, que comprende ademÆsun recubrimiento sobre el nCicleo.

12. El mØtodo de la reivindicación 7, en donde el recubrimiento es un recubrimiento de liberación controlada.

10 13. Un mØtodo para reducir incidencias de crisis convulsivas inducidas por bupropion que comprende:

administrar una cantidad farmacØuticamente efectiva de bromhidrato de bupropion a tin
sujeto que necesita la administración de bupropion;
en donde las incidencias de crisis convulsivas inducidas por bupropion que resultan de la adrninistración de bromhidrato de bupropion son inenores que las incidencias de crisis

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convulsivas inducidas por bupropion que resultan de Ia administraciOn de una cantidad molar equivalente de clorhidrato de bupropion.

14. El mØtodo de la reivindicación 13, en donde las crisis convulsivas inducidas por bupropion que resultan de la administración de bromhidrato de bupropion son menos graves que las crisis convulsivas inducidas por bupropion que resultan de la adrniriistración de una cantidad molar equivalente de clorhidrato de bupropion.

15. Un mØtodo Para reducir incidencias de crisis convulsivas inducidas por bupropion que comprende:
administrar una cantidad farmacØuticamente efectiva de bromhidrato de bupropion a un
sujeto que necesita la administración de bupropion;
en donde la administración de aproximadamente 100 mg/kg del bromhidrato de bupropion a

40 una primera rata resulta en menos incidencias de crisis convulsivas inducidas por bupropion
en comparación con las incidencias de crisis convulsivas inducidas por bupropion que
resultan de la administraciOn de una cantidad molar equivalente de clorhidrato de bupropion a
una segunda rata; y
en donde las incidencias de las crisis convulsivas inducidas por bupropion en la primera y
segunda rata se miden rnediante un anÆlisisde electroencefalograma utilizando un electrodo
profundo implantado en el hipocampo.

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16. Un mØtodo Para reducir las incidencias de con\rulsiones inducidas por bupropion que comprende la administración conjunta de una sal de bromuro con una sal de bupropion, en
donde la sal de bromuro se administra en una cantidad menor a aproximadamente 3,5 mg/kg.

IT El mØtodo de la reivindicación 16, en donde la sal de bromuro es bromuro de sodio.

18. El mØtodo de la reivindicaciOn 16, en donde la sal de bupropion es clorhidrato de
bupropion.

19. Una composiciOn que comprende bromhidrato de bupropion y a! menos un excipiente farmacØuticamente aceptable;

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en donde la administración de aproximadamente 100 mg/kg de un bromhidrato de bupropion utilizado para fabricar la composición a una primera rata resulta en menos incidencias yb gravedad de crisis convulsivas inducidas por bupropion en comparación con las incidencias y/o gravedad de crisis convulsivas inducidas por bupropion que resultan de la administración de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata; y
en donde las incidencias y/o la gravedad de las crisis convulsivas inducidas por bupropion se miden mediante un anÆlisis deelectroencefalograma utilizando un electrodo profimdo implantado en el hipocampo.

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RESUMEN DE LA INVENCION

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Se describen formulaciones de bromhidrato de bupropion, asI corno tambiØn su uso para el tratamiento de afecciones.

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t,.…1 .. I’

Lubricacion4

CO presiôn

Recubrimiento (Recubrimiento Ethocel! Recubrimiento de liberaciOn controlada

Recubrimiento (Recubrimiento final! Barrera contra la humedad)

Figura 1

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3155

- Compresora Beta
- Punzones de 9mm para comprlmidos de 300mg
- Punzones de 7mm para comprlmldos de 150mg Parªmetros:

- Espesor antes de comprimir:
2mm

- Espesor de control: 15-2Omm
- Espesor de Ilenado: 7-8mm
- Presiön de sobrecarga: 15-2,0 toneladas
- Comprimidos por minuto: 450-500
- Velocidad del alimentador: 1-2

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Figura 11
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CD

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Tiem po (horas)

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Figura 19

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80,00-

0

uuuu co
- rrg AP U-2&M AP A 30n- AP 0---32n API

40,00

2000

000- -’

0 2 4 6 8 10 12 14 16 18
Tiempo(horas)

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Perfiles de disoluciOn comparativos de comprimidos de Bupropion HBr XL 348mg en HCI Q,IN versus 5 20 40% de EtoH en HCl 0,IN

39,0
 0-- MCI 0,IN

36,0 MCI 0,IN (60%)- EtOH (40%)
33,0 __ MCI 0,IN (80%) EtOH (20%)

30,0, ______ MCI 0,1N (95%)- ROM (5%)

9,0

8,0

3,0

0,01 0
0,0 15,0 30,0 45,0 60,0 75,0 90,0 105,0 120,0 135,0

Tiempo (minutos)

Figura 30

S

Perfiles de disoluición comparativos de comprimidos de Bupropion HBr XL 17.4mg en HCI 0,1N versus 5,20 y4O% de FtoH en HCI 0,1N

0 .36,0

2
0
In I
O
12.0
9.0

3,11

0,0 15,0 30,0 45,0 60,0 75,0 90,0 105,0 120,0 135,0
Tiempo (minutos)

.9,0

30

7,0

- - - . HCI 0,IN
- _- MCI O,IN (60%)-
__ *...0,1N(80%)Et0H
MCI 0,1N (95%)-

EtOH (40%)
(20%)
EtOH (5%) ____________________________

6,0

Figura 31

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Perfiles de disOtUckn comparativos de comprimidos de Bupropion HBr XL 348mg en HCI 0,IN versus 5, 20 40% de EtoH en HCI 0,IN

3

2

0

2

L
1!

0,0 15,0 30,0 45,0 60,0 75,0 90,0 105,0 ,0 135,0

Tiempo (minutos)

ag

3

120

3,0
 0--HCIO,IN

3 lId 0 IN (60%)- EtOH ’40%

,0

__- HCI 0,IN (80%)- EtOH (20%)
- .- HCI 0 IN (95%) EtOH (5%)

0,0

Figura 32

I

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Estudio B06-756PK-10121 (3230)
Concentraciones medias de eritroamino alcohol de bupropion en plasma en estado estacionario (n38)

160-
-.9-Gomprimidos de Bupropion HUr XL 348mg, Lote 06C159P  0 Comprimidos de Welibutrin XL 300mg, Lote 06C090P

140- 0

IR E0 CO

OE 120

IL100

60

Tiempo (hora)

Figura 36: Concentración de eritroamino alcohol de btipropion en plasma media con respecto al tieinpo para el Estudo B06-756PK-10121 (3230)

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Estudio B06-756PK-10121 (3230)
Compuesto medlo ponderado con actividad farmacológica en plasma en estado estacionarlo (n=38)

6,0
Comprimidos de Buproplon HBr XL 348mg, Lote 06C159P
 0-- Comprimidos de Wellbutrin XL 300mg, Lote 06C090P

_. 5,0

T

i:

li4,0

2,0

1,0

Tiempo (hora)

Figura 37: CompLiesto ponderado con actividad farmacolØgica (FAWC) en plasma medio con respecto al tiempo para el Estudio B06-756PK-10121 (3230)

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Estudio B06-755PK-10121 (3228) Concentraciones medias de hidroxibupropion en plasma en
dosis (mica (n=46)

800

I
600 .--- 2 x Comprmidos de Bupropion HBr XL 174 mg, Lote 060029P
2 O I X Comprimido de Bupropion HUr XL 348mg Lote 060159P

CL

x 400-

0 24 46 72 96 120 144 168 192 216

Tiempo (hora)

Figura 40: Concentración de hidroxibupropion en plasma media con respecto al tiempo para el Estudio B06-755PK-10121 (3228)

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Estudio B06-755PK-10121 (3228) Concentraciones medias de eritroamino alcohol de bupropion en
plasma en dosis unica (n=46)

50-

o 40 -- 2 x Gomprimidos de Bupropion I-IBr XL. 174 mg, Lote 06DQ29P
E 0-- 1 x Comprimido de Bupropion HBr XL 348mg, Lote 06C159P
c

.2 30 CL
C0.

:22

1120

10

0
0 24 48 72 96 120 144 168 192 216

Tiempo (hora)

Figura 42: Concentración de eritroamino alcohol de bupropion en plasma media con respecto al tiempo para el Estudio B06-755PK-10121 (3228)

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Estudlo B06-755PK-10121 (3228)
Compuesto ponderado con actividad farmacológica en plasma
en dosis ünica (n46)

2,5

- . 2,0
.2: 2 x Comprimidos de Buproplon HBF XL 174 my, Lote 06D029P 1 x Comprimido de Bupropion HBr XL 348mg, Lote 06C159P

w2 1,5

oe
0
10
CL V
0
(U
0,5

0,0 I
0 24 48 72 96 120 144 168 192 216

Tiempo (hora)

Figura 43: Compuesto ponderado con actividad farmacoiógica (PAWC) en plasma medio con respecto al tiempo para ci Estudio B06-755PK-10121 (3228)

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Estudio B06-754PK-10121(3229) Concentraciones medias de bupropion en plasma en dosis Unica

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Estudio B06-754PK-10121 (3229) Concentraciones medias de hidroxibupropion en plasma en dosis
Unica (n=48)
800

 J
E
C)
C

g 600
- _ Compnmidos de Bupropion HBr XL 348 mg, Lote 06C159P, alimentados  0 Comprimidos de Bupropion HBr XI. 348 mg, Lote 06C159P, en ayuno jo
2 400

C,
C

 0

20: I

I

0 24 48 72 96 120 144 168 192 216

Tiempo (hora)

Figura 46: Concentración de hidroxibupropion cii plasma media con respecto al tiempo para el Estudio B06-754PK-10121 (3229)

0-i

200
2 C

I

0

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Estudio B06-754PK-10121 (3229)
Concentraclones medias de treoamino alcohol de buproplon en
plasma en dosis ünica (n=48)
300

Gomprumidos de Bupropion HBr XL 348 mg Lote 06C169P aHmentados
0 Comprimidos de Bupropion HBr XL 348 mg Lote 06C159P, en ayuno

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Estudio B06-754PK-10121 (3229)
Concentraciones medias de eritroamino alcohol de bupropion en

plasma en dosis ünica (n=48)

50

40 -- Comprimidos de Bupropion HBr XL 348 mg, Late 06C159P, alimentados
 0-- Comprimidos de Bupropion HBr XL 348 mg. Late 06C159P, en ayuno
cc

ES
- c

.2 30
00

’0

h20

o C

0

0 24 48 72 96 120 144 168 192 216

Tiempo (hora)

Figura 48: Concentración de eritroamino alcohol de bupropion en plasma media con respecto al tiempo para ci Estudio B06-754PK-10121 (3229)

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Estudio de doble intercambio con varias dosis en ayunas Concentraciones medias de treoamino alcohol de bupropion en
plasma (n=29)
1400-

Comprimido de Bupropion HBr XL 522 mg, Lote 06M119P

1200 -0 3x Comprimidos de Bupropion HBr XL 174 mg, Lote 06M062)
0 J

1I600

400- 0

0
U

200-

0
0 4 8 12 16 20 24

Tiempo (horas)

Figura 52: Concentraciôn de treoamino alcohol de bupropion en plasma media con respecto al tiempo para ci Estudio B06-802PK-10121 (AA40055)

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Estudlo de doble intercambio con varias dosis en ayunas Compuesto medlo ponderado con actividad farmacológica en
plasma (n=29)
8

..__ Comprimido de Bupropion HBr XL 522 mg, Lote 06M119P
- .0 3 x Comprimidos de Bupropion HBr XL 114 mg, Lote 06M062)

2 6-

6 to
CL E

41

Tiempo (horas)

Figura 54: Compuesto ponderado con actividad farrnacológica PAWC) en plasma medio con respecto al tiempo

In I flP1M I IIJiIML I I

I internatIonal application No

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9128 A61K31/135 A61K33/00

According to International Patent Classification (IPO) or to both national classification and]PC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, FSTA, BIOSIS

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later than the priority date claimed document member of the same patent family

Date of the actual completion of the international search Date of mailing of the international search report

4 May 2009 27/05/2009

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INTERNATIONAL SEARCH REPORT

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES InclustnayComercio EXTRACTO PARA PUBLICACION
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No. de solicitud PCT/EP2008/060361

(54) Titulo: BROMHIDRATO DE BUPROPION V APLICACIONES TERAPEUTICAS

Reivindicaciôn(es):

1, Una composición que comprende bromhidrato de
bupropion y al menos un excipiente farmacØuticamente
aceptable;
en donde la administración de una cantidad de un bromhidrato
de bupropion a una primera rata resulta en menos incidencias de crisis convulsivas inducidas por bupropion y/o crisis convulsivas inducidas por bupropion menos graves en comparaciôn con las incidencias y/o gravedad de las crisis convulsivas inducidas per bupropion que resultan de la administraciOn de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata; y
en donde las incidencias y/o la gravedad de las crisis convulsivas inducidas per bupropion se miden mediante un anÆlisis de electroencefalograma utilizando un electrode profundo implantado en el hipocampo.

2. La composiciOn de la reivindicaciOn 1, que se
encuentra en forma de comprimido.

3. La composicion de la reivindicaciOn 1, que es una
formulaciôn de liberaciOn modificada.

4. La composición de la reivindicación 1, que se
encuentra en forma de comprimido y en donde el bromhidrato de bupropion se encuentra dentro de un nUcleo del comprimido, que comprende ademÆs un recubrimiento sobre el ncIeo.

5. La composiciOn de La reivindicaciOn 4, en donde el
recubrimiento es un recubrimiento do liberaciOn controlada.

6. Una composiciOn que comprende bromhidrato de
bupropion y al menos un excipiente farmacØuticamente aceptable;
en donde la administraciOn de aproximadamente 100 mg/kg de un bromhidrato de bupropion a una primera rata resulta on menos incidencias y/o gravedad do crisis convulsivas inducidas por bupropion en comparación con las incidencias y/o gravedad do crisis convulsivas inducidas por bupropion que resultan do la administraciôn de una cantidad molar equivalente de clorhidrato de bupropion a una segunda rata; y en donde las incidencias y/o La gravedad de Las crisis convulsivas inducidas per bupropion so miden mediante un

anâlisis de electroencefalograma utilizando un electrodo profundo implantado en el hipocampo.

7. Un mØtodo para tratar un sujeto con riesgo de padecer
crisis convulsivas inducidas per bupropion quo necesita un tratamiento con bupropion, comprendiendo el mØtodo; administrar una composiciôn que comprende bromhidrato de bupropion a dicho sujeto en una cantidad suficiente para tratar dicho sujeto.

8. El mØtodo de la reivindicación 7, en donde la
composición comprende una cantidad de bromhidrato de bupropion que se selecciona de 174 mg, 348 mg y 522 mg.

9. El metodo de La reivindicaciOn 7, en donde la
composición so encuentra en forma de comprimido y la administraciOn comprende la administración oral.

10. El mØtodo de la reivindicación 7, en donde la
composición es una formulaciOn de!iberaciOn modificada

11. La composiciOn de la reivindicaciOn 7, en donde la
composición so encuentra en forma de comprimido y en donde el bromhidrato de bupropion se encuentra dentro de un nUcleo del comprimido, que comprende ademÆs un recubrimiento sobre el nücleo.

12. El mØtodo de la reivindicaciôn 7, en donde el
recubrimiento es un recubrimiento do Liberaciôn controlada.

13. Un mØtodo para reducir incidencias de crisis
convulsivas inducidas per bupropion quo comprende: administrar una cantidad farmacØuticamente efectiva de bromhidrato de bupropion a un sujeto que necesita la administraciÆn debupropion;
en donde las incidencias de crisis convulsivas inducidas per bupropion que resultan de La administraciOn de bromhidrato de bupropion son menores que Las incidencias de crisis convulsivas inducidas per bupropion que resultan de la administración de una cantidad molar equivalente do clorhidrato de bupropion.