OPS.

Organizacion CSA Ltda

OF

EXP N.

PCT

07-136836

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-136836- -00000-0000
Fecha: 2007-12-27 18:12:00 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 954

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **BIOVAIL LABORATORIES INTERNATIONAL S.R.L.**
sociedad constituida y existente bajo las leyes de Barbados.

Dirección: Chelston Paerk,
Building 2, Ground Floor,
Collymore Rock,
St. Michael,
Barbados

Domicilio: Collymore Rock,
St. Michael,
Barbados

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. **Werner OBEREGGER**,
6653 Harlow Road,
Mississauga,
Ontario L5N 4T4,
Canadá

2. **Fang ZHOU**,
5337 Sammie Kay Lane,
Centreville,
Virginia 20120,
Estados Unidos de América

3. **Paul MAES**,
Toronto,
Ontario,
Canadá

4. **Stefano TURCHETTA**
Patricia,
Italia

5. **Graham JACKSON**
Dublin,
Irlanda

6. **Pietro MASSARDO**
Patricia,
Italia

7. **Mohammad Ashty SALEH**
223 Gatwick Drive,
Oakville,
Ontario L6H 6T6,
Canadá

5 PCT (86)

Solicitud Internacional No. PCT/US2006/024832 Fecha: 27 de junio de 2006
Publicación Internacional No. WO 2007/002597 A2 Fecha: 4 de enero de 2007

6 Título (54)

FORMULACIONES DE UNA SAL DE BUPROPION DE LIBERACIÓN MODIFICADA

7 **Clasificación Internacional (51)** A61K 031/195

8 **Prioridad** SI☒ NO☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	27 de junio de 2005	60/693,906

9 **Comprobante de pago No.:** 07-100,353 **Fecha:** 10 de diciembre de 2007

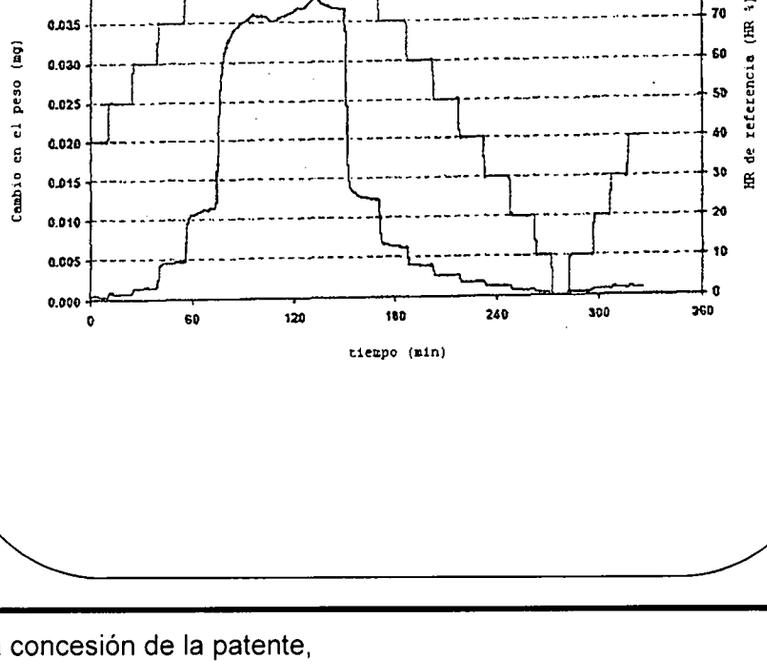
10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 482.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA

FIGURA 1



12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

AHP

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2007-002597 A2

   Descripción:

   Páginas 339 en el idioma original

   Páginas 475 en español

   Reivindicaciones: Número (s) 83

   Figuras: Número (s) 69

2. ☒ **Forma PCT/IB/306.** Notificación de la inscripción del Inventor **Mohammad Ashty SALEH**

3. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

5

1857

15439
77566

BIOVAIL LABORATORIES INTERNATIONAL SRL

CERTIFICATE

I, **ARLENE L. FONG** of Biovail Laboratories International SRL (the Society) of Chelston 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 5th day of May, 2006.

BIOVAIL LABORATORIES INTERNATIONAL SRL

Arlene L. Fong
Manager and Secretary

BARBADOS

NOTARIAL CERTIFICATE

I, **GODFREY WINSTON HINDS** Notary Public in and for the Island of Barbados do hereby **CERTIFY** that on the day and the date hereof personally came and appeared before me a female person who identified herself to 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 of Biovail Laboratories International SRL which attests to the above-noted statement.

DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL

29 DIC 2007

PABLO MENDEZ
MAY

GIVEN under my hand and Notarial Seal of Office this 05 day of ~~April~~, 2006.

Barbados $10

Notary Public in and for the Island of Barbados
GODFREY W. HINDS
DEPUTY REGISTRAR AND AS SUCH
A NOTARY PUBLIC IN
AND FOR BARBADOS
CORPORATE AFFAIRS AND
INTELLECTUAL PROPERTY OFFICE

CAVELIER
ABOGADOS
EDIFICIO
CARRE
BO

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PABLO [illegible]ENDEZ BARAJAS
NOTARIO (E)

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1. Country: BARBADOS

This public document

2. has been signed by GODFREY WINSTON HINDS

3. acting in the capacity of ACTING DEPUTY REGISTRAR AND AS SUCH A NOTARY PUBLIC IN AND FOR THE ISLAND OF BARBADOS

4. bears the seal/~~stamp~~ of THE NOTARY PUBLIC OF BARBADOS

Certified

5. at BRIDGETOWN, BARBADOS 6. the MAY 08, 2006

7. by HUGHLAND ST. CLAIR ALLMAN, ACTING CHIEF OF PROTOCOL

8. N°. 657/2006

MINISTRY OF FOREIGN AFFAIRS BARBADOS

9. ~~Seal~~/stamp 10. Signature

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8,- COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, 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.

REPRESENTACION Y PODER

REPRESENTATION AND POWER OF ATTORNEY

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

BIOVAIL LABORATORIES INTERNATIONAL SRL

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

Collymore Rock, St.Michael, Barbados, West Indies

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y GERMAN CAVELIER, tpa. 832, domiciliados en la Carrera 4a N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en

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, Bogotá, 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 their turn, 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 contentious and judicial, as well as before Arbitration Court, in all

DE BOGOTA, HAGO CONSTAR QUE LA
QUE HE TENIDO A LA VISTA
26 OCT 2007
NOTARIO (E)

© CAVELIER ABOGADOS

odo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, 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 of licenses, 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 hoy/Given and signed this 5th MAY 2006

en/in BRIDGETOWN, BARBADOS

por/by ARLENE FONG

MANAGER & SECRETARY

Firma/Signature

BIOVAL LABORATORIES INTERNATIONAL SRL

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

2 DIC 2007

PABLO [illegible]ENDEZ MARAJAS
NOTARIO (E)

© CAVELIER ABOGADOS

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CERTIFICACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de

es auténtica; que el signatario desempeña actualmente el cargo de

de la compañía **BIOVAIL LABORATORIES INTERNATIONAL SRL**

sociedad que actualmente existe y está organizada de acuerdo a las leyes de

Barbados

que la dirección de dicha compañía 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 _____

País _____

Hoy _____ del mes 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

of the company **BIOVAIL LABORATORIES INTERNATIONAL SRL**

a company currently existing and organized under the laws of

Barbados

that the address is

Chelston 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 of the 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: .....

Certified

5. at: ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

.....

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA

26 DIC 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

© CAVELIER ABOGADOS

9

FORM 2

SOCIETY NO. 443

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS

CERTIFICATE OF ORGANISATION

BIOVAIL LABORATORIES INTERNATIONAL SRL

Name of Society

I hereby certify that the above-mentioned Society, the Articles of Organisation of which are attached, was organised under the Societies with Restricted Liability Act of Barbados.

Dep. Registrar of Corporate Affairs
and Intellectual Property

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TENIDO A LA VISTA
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

December 21st, 2004

Date of Organisation

Form 15

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS

REQUEST FOR NAME SEARCH AND NAME RESERVATION

1. Name, Address, telephone number and facsimile number of person making request:

Liza A. Harridyal-Sodha
The Savannah Business Centre
Suite 130, Hastings
Christ Church, Barbados

Telephone Number: **246-228-9888**
Facsimile Number: **246-228-9382**

2. Proposed name or names in order of preference
   (a) **BIOVAIL LABORATORIES INTERNATIONAL SRL**
   (b)
   (c)

3. Main types of business the Society carries on or proposes to carry on:
   (a) **An International Society in accordance with the Societies with Restricted Liability Act 1995-7.**
   (b) **The Society is formed for the 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

5. First name available to be reserved: Yes ☐ No ☐

6. Name is for:
   Organisation

7. If for a change of name, state present name of Society:
   Not Applicable

For Ministry use only

Name reserved until (specify date)

1 ☐
2 ☐
3 ☐

APPROVED
For Director

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

See attached letter if name is not reserved

Date received:

2004-12-21

Request received by:

D. Block

NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

CONSENT

BIOVAIL LABORATORIES INCORPORATED, amalgamated under the Companies Act Cap. 308 of the laws of Barbados on the 16th day of March, 2004, hereby consents to the use of the name **BIOVAIL LABORATORIES INTERNATIONAL SRL** and any variation thereof acceptable to the Registrar by the proposed body corporate, Articles of Organization for which are being filed by Liza A. Harridyal-Sodha and others.

IN WITNESS WHEREOF BIOVAIL LABORATORIES INCORPORATED has hereunto executed this consent under the hands of its proper Officer in that behalf.

Dated at Bridgetown, Barbados this 21st day of December, 2004.

BIOVAIL LABORATORIES INCORPORATED

By: _____
Arlene Fong
Director

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

CONSENT

BIOVAIL HOLDINGS LTD, incorporated under the Companies Act Cap. 308 of the laws of Barbados on the 23rd day of January, 2001, hereby consents to the use of the name **BIOVAIL LABORATORIES INTERNATIONAL SRL** and any variation thereof acceptable to the Registrar by the proposed body corporate, Articles of Organization for which are being filed by Liza A. Harridyal-Sodha and others.

IN WITNESS WHEREOF BIOVAIL HOLDINGS LTD has hereunto executed this consent under the hands of its proper Officer in that behalf.

Dated at Bridgetown, Barbados this 21st day of December, 2004.

BIOVAIL HOLDINGS LTD

By: _____
Arlene Fong
Director

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PA[illegible] MENDEZ BARAJAS
NOTARIO (E)

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

13

Form 3

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS
(Section 23(1) and (2))

NOTICE OF ADDRESS
OR
NOTICE OF CHANGE OF ADDRESS OF REGISTERED OFFICE

1. **Name of Society**

   BIOVAIL LABORATORIES INTERNATIONAL SRL

   Society Number 443

2. **Address of Registered Office**

   Building No. 2, Chelston Park
   Collymore Rock
   St. Michael
   Barbados

3. **Mailing Address**

   Building No. 2, Chelston Park
   Collymore Rock
   St. Michael
   Barbados

4. **If change of address, give previous address of Registered Office.**

   N/A

5.

Date	Signature	Title
December 21, 2004	**Liza A. Harridyal-Sodha**	**Organiser**

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CORRESPONDE FIEL Y QUE HE TENIDO A LA VISTA EL ORIGINAL
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

For Ministry use only

Society Number: 443

Filed: 2004-12-21

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

Form 6

SOCIETIES WITH RESTRICTED LIABILITY OF BARBADOS
(Sections 18)

NOTICE OF MANAGERS
OR
NOTICE OF CHANGE OF MANAGERS

1. Name of Society

BIOVAIL LABORATORIES INTERNATIONAL SRL

Society Number 443

2. Notice is given that on the day of , the following person(s) was / were appointed director(s)

Name	Residential Address	Occupation
	N/A	

3. Notice is given that on the day of , the following person(s) ceased to hold office as manager(s)

Name	Residential Address
	N/A

4. The managers of the society as of this date are

Name	Residential Address	Occupation
Eugene N. Melnyk	Beach House, Crane, St. Philip, Barbados	Business Executive
Arlene L. Fong	2 South Point View, Enterprise, Christ Church, Barbados	Business Executive
Paul W. Haddy	B26 Graeme Hall Park, Christ Church, Barbados	Business Executive

5.

Date	Signature	Title
December 21, 2004	**Liza A. Harridyal-Sodha**	**Organiser**

NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
NOTARIO (E)

For Ministry use only
Society Number: 443

Filed: 2004-12-21

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS

CONSENT TO ACT AS REGISTERED AGENT

I, **LIZA A. HARRIDYAL-SODHA**
Name of Attorney

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

hereby consent to act as the Registered Agent for **BIOVAIL LABORATORIES INTERNATIONAL SRL** pursuant to the Appointment of Registered Agent dated the **21st of December, 2004** filed herewith.

Dated this 21st day of December, 2004

Signature of Registered Agent

WITNESS:

Name: RUTH CAMPBELL

Signature: Ruth Campbell

Address: Lovell Rd.
Massiah St.
St. John

Occupation: Secretary

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE FUE TENIDO A LA VISTA
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

Form 19

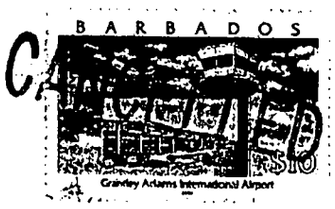
THE STAMP ACT
2004 -12-21
DULY STAMP
WITH $ 10.00
DEPUTY REGISTRAR
& ADJUDICATOR
BARBADOS.

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS

Section (50)

APPOINTMENT OF REGISTERED AGENT

Know all men by these present that **BIOVAIL LABORATORIES INTERNATIONAL SRL** 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 do all the acts and to execute all deed and other instruments relating 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 will be binding on the Society for all purposes.



Date	Signature	Title
December 21, 2004	**Liza A. Harridyal-Sodha**	**Organiser**

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
28 DIC 2004
PABLO MENDEZ BARAJAS
NOTARIO (E)

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

Form 1

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS
(Section 5)

ARTICLES OF ORGANISATION

1. Name of Society

   BIOVAIL LABORATORIES INTERNATIONAL SRL

   Society Number 443

2. The purpose for which the Society was formed
   The Society is formed for the purposes of owning and operating a pharmaceutical business, in accordance with the Societies with Restricted Liability Act 1995-7.

3. The duration of the Society (shall not exceed 50 years).
   Fifty (50) years.

4. The registered office of the Society in Barbados
   Building No. 2, Chelston Park, Collymore Rock, St. Michael, Barbados

5. The name and address of the Society's agent in Barbados
   Liza A. Harridyal-Sodha
   Suite 130, The Savannah Business Centre, Hastings, Christ Church, Barbados

6. The classes and any maximum number of quotas that the Society is authorized to issue
   The Society is authorized to issue an unlimited number of quotas designated as Common Quotas.

7. Restriction on transfer of quotas
   The annexed Schedule I is incorporated into this form.

8. Restriction if any on business the Society may carry on
   The Society shall not engage in any business other than the business of an International Society with Restricted Liability as defined in Societies with Restricted Liability Act 1995-7

9. Other provisions if any
   The annexed Schedule II is incorporated into this form.

10. Signatories: Date: December 21, 2004

Name	Address	Signature
Liza A. Harridyal-Sodha	**#6 Gunsite, Brittons Hill, St. Michael, Barbados**	

For Ministry use only
Society Number: 443

Filed: 2004-12-21

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
PABLO MENDEZ G[illegible]AS
NOTARIO (E)

REGISTERED
SIGNATURE D' B
DATE 2004-12-21
CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

Form 1

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS

Section (5)

SCHEDULE I TO ARTICLES OF ORGANISATION

Name of Society **Society No.** 443

BIOVAIL LABORATORIES INTERNATIONAL SRL

7. ***Restrictions on Transfer of Quotas:***

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 is not effected in the manner prescribed by the Articles or the SRL Act.

Name	Address	Signature
Liza A. Harridyal-Sodha	**#6 Gunsite, Brittons Hill, St. Michael, Barbados**	

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

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Form 1

SOCIETIES WITH RESTRICTED LIABILITY ACT OF BARBADOS

Section (5)

SCHEDULE II TO ARTICLES OF ORGANISATION

Name of Society **Society No.** 143

BIOVAIL LABORATORIES INTERNATIONAL SRL

9. ***Other provisions if any:***

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 the 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-Sodha	**#6 Gunsite, Brittons Hill, St. Michael, Barbados**	

REGISTERED CORPORATE AFFAIRS AND INTELLECTUAL PROPERTY OFFICE

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

28 DIC 2007

[illegible] MENDEZ BARAJAS
NOTARIO (E)

TRADUCCIÓN OFICIAL 150/2006 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL DE ACUERDO CON EL CUAL **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 CONSTITUCIÓN

BIOVAIL LABORATORIES INTERNATIONAL SRL

Por la presente certifico que la sociedad arriba mencionada, cuyo certificado de CONSTITUCIÓN se adjunta, fue creada de acuerdo con la Ley de Barbados sobre sociedades con responsabilidad restringida.

Firmado: Registrador de asuntos societarios y propiedad intelectual

Fecha de constitución: 21 de diciembre de 2004.

SOLICITUD DE BÚSQUEDA Y DE RESERVA DE NOMBRE

1. Nombre, dirección y número de teléfono de la persona que haga la solicitud:

LIZA A. HARRIDYAL-SODHA

THE SAVANNAH BUSINESS CENTRE

SUITE 130, HASTINGS

CHRIST CHURCH, BARBADOS

Número de teléfono: 246-228-9888

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
16 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

2. Nombre o nombres propuestos en orden de preferencia

(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 está formada con el objeto de poseer y operar una empresa farmacéutica de acuerdo con la Ley de sociedades con responsabilidad restringida 1995-7**

4. Derivación del nombre: empresa matriz

5. Primer nombre disponible para reservar: (DATO EN BLANCO)

6. El nombre es para ORGANIZACION

7. En caso de que sea para cambio de nombre, informar el nombre actual de la empresa: No se aplica

PARA USO SOLO POR EL MINISTERIO

APROBADA.

FECHA DE RECIBO: 21 DE DICIEMBRE DE 2004.

SOLICITUD RECIBIDA POR D. BLACK.

CONSENTIMIENTO

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007

BIOVAIL LABORATORIES INCORPORATED, fusionada de acuerdo con la ley de Compañías Capítulo 308 de las leyes de Barbados el 16 de marzo de 2004, por la presente consiente en usar el nombre BIOVAIL LABORATORIES INTERNATIONAL SRL y cualquier variación aceptable del mismo para el registrador, con respecto a su ente

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corporativo. Su documento de constitución es radicado por LIZA A. HARRIDYAL-SODHA y otros.

En testimonio de lo cual, BIOVAIL LABORATORIES INCORPORATED ha firmado este consentimiento a través de su funcionario adecuado.

Fechado en Bridgetown, Barbados, 21 de diciembre de 2004

BIOVAIL LABORATORIES INCORPORATED

POR: ARLENE FONG, DIRECTOR.

CONSENTIMIENTO

BIOVAIL HOLDINGS LTD, constituida de acuerdo con la ley de compañías Capítulo 308 de las leyes de Barbados el 23 de enero de 2001, por el presente consiente en usar el nombre BIOVAIL LABORATORIES INTERNATIONAL SRL, y cualquier variación del mismo aceptable para el Registrador. Los Artículos de CONSTITUCIÓN son radicados por LIZA A. HARRIDYAL-SODHA y otros.

En testimonio de lo cual, BIOVAIL HOLDINGS LTD ha firmado este consentimiento mediante el funcionario adecuado.

Fechado en Bridgetown, Barbados hoy 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)

NOTIFICACIÓN DE DIRECCIÓN

O

NOTIFICACIÓN DE CAMBIO DE DIRECCIÓN DE OFICINA REGISTRADA

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

06 DIC 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

1. NOMBRE DE LA SOCIEDAD:

BIOVAIL LABORATORIES INTERNATIONAL SRL

SOCIEDAD NÚMERO 443

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2. DIRECCIÓN DE OFICINA REGISTRADA

BUILDING NO. 2, CHELSTON PARK

COLLYMORE ROCK

ST. MICHAEL

BARBADOS

3. DIRECCIÓN POSTAL

BUILDING NO. 2, CHELSTON PARK

COLLYMORE ROCK

ST. MICHAEL

BARBADOS

4. EN CASO DE TRATARSE DE CAMBIO DE DIRECCIÓN, INFORMAR LA DIRECCIÓN PREVIA DE LA OFICINA REGISTRADA (NO SE APLICA)

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FECHA:

21 DE DICIEMBRE DE 2004.

FIRMA: LIZA A. HARRIDYAL-SODHA

TÍTULO: FUNDADOR

SOLO PARA USO DEL MINISTERIO

SOCIEDAD NÚMERO 443

RADICADO EL 21 DE DICIEMBRE DE 2004

NOTIFICACIÓN DE GERENTES

O

NOTIFICACIÓN DE CAMBIO DE GERENTES

1. NOMBRE DE LA SOCIEDAD

BIOVAIL LABORATORIES INTERNATIONAL SRL

SOCIEDAD NÚMERO 443

2 (DATOS EN BLANCO)

3. (DATOS EN BLANCO)

4. LOS GERENTES DE LA SOCIEDAD A ESTA FECHA SON

COMO NOTARIO SEXTO (E) DEL CIRCUITO DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PABLO MENDEZ BARAJAS
NOTARIO (E)

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

FECHA: 21 DE DICIEMBRE DE 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 aquí.

Fechado hoy 21 de diciembre de 2004.

Firma del agente registrado.

TESTIGO:

NOMBRE: RUTH CAMPBELL, DIRECCIÓN LOVELL RD, M STR, ST. JOHN

OCUPACIÓN: SECRETARIA

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA
28 DIC 2007
PABL[illegible] MENDEZ BARAJAS
NOTARIO (E)

NOMBRAMIENTO DE AGENTE REGISTRA[illegible]

25

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 continuación llamaremos la Sociedad) por el presente nombra a LIZA A. HARRIDYAL-SODHA como su agente registrado domiciliado en SUITE 130, The Savannah Business Centre, Hastings, Christ Church, Barbados, para actuar como tal, y quien puede ser demandado, demandar 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 jurídicas 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 ámbito de este nombramiento. Se declara que las notificaciones con respecto a demandas y actuaciones contra la sociedad y con respecto a notificaciones jurídicas al agente registrado serán obligatorias para la sociedad para todo propósito.

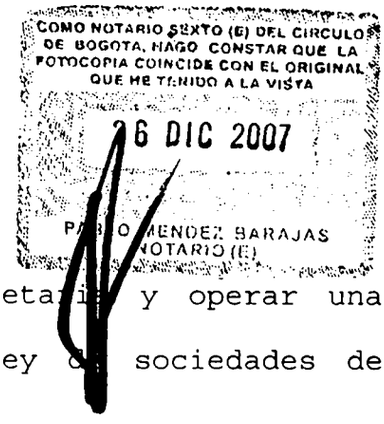
FECHA: 21 DE DICIEMBRE DE 2004. FIRMADO: LIZA A. HARRIDYAL-SODHA, ORGANIZADORA.

ARTÍCULOS DE CONSTITUCIÓN

1. NOMBRE DE LA SOCIEDAD:

BIOVAIL LABORATORIES INTERNATIONAL SRL

SOCIEDAD NÚMERO 443



2. El objeto social de la sociedad es

La sociedad se constituye para ser propietaria y operar una empresa farmacéutica de acuerdo con la ley de sociedades de responsabilidad restringida 1995-7

3. La duración de la sociedad será por CINCUENTA AÑOS.

4. La oficina registrada de la sociedad en Barbados es

Building No. 2, Chelston 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 número máximo de cuotas que la sociedad está autorizada a emitir

La sociedad está autorizada a emitir un número ilimitado de cuotas, llamadas cuotas comunes.

7. Restricción en la transferencia de cuotas:

El Cuadro I adjunto queda incorporado a esta forma.

8. Restricción (de existir) relacionada con los negocios que puede realizar la empresa

La sociedad no puede participar en ningún 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	DIRECCIÓN	FIRMA
Liza A. Harridyal-Sodha	#6 Gunsite, Brittons Hill, St. Michael, Barbados	

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOCOPIA ES IGUAL AL ORIGINAL QUE ME FUE PUESTO A LA VISTA
28 DIC 2007
PABLO [illegible] BARAJAS
NOTARIO (E)

PARA USO DEL MINISTERIO SOLAMENTE:

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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 ARTÍCULOS DE CONSTITUCIÓN

NOMBRE DE LA SOCIEDAD:

BIOVAIL LABORATORIES INTERNATIONAL SRL

SOCIEDAD NÚMERO 443

7. RESTRICCIONES A LA TRANSFERENCIA DE CUOTAS:

De acuerdo con la ley de sociedades con responsabilidad restringida, 1995-7 (Ley SRL) un beneficiario de transferencia de cuotas no se volverá miembro, ni participará en la administración de los asuntos empresariales de la sociedad a menos que todos los miembros expresen unánimemente su consentimiento con la transferencia. Ninguna transferencia de cuotas en el capital de la sociedad se registrará sin contar con la aprobación de la junta de gerentes de la sociedad o de un comité de la junta de gerentes de la sociedad evidenciada por resolución. La junta de gerentes rechazará el registro de transferencia de cuotas que no esté autorizado por los artículos de la Ley SRL o que no se haya efectuado en la forma estipulada por los artículos de la Ley SRL.

NOMBRE	DIRECCIÓN	FIRMA
LIZA A. HARRIDYAL-SODHA	#6 GUNSITE, BRITTONS HILL, ST. MICHAEL, BARBADOS	ILEGIBLE

COMO NOTARIO (E) DEL CIRCULO, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE DADO A LA VISTA
26 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

ANEXO II A LOS ARTÍCULOS DE CONSTITUCIÓN

NOMBRE DE LA SOCIEDAD: BIOVAIL LABORATORIES INTERNATIONAL SRL

SOCIEDAD 443

9. Otras estipulaciones:

Esta sociedad internacional de responsabilidad restringida no podrá:

A. 1. Adquirir o poseer tierras en Barbados, diferentes de los terrenos requeridos para negocios por vía de convenio de alquiler financiero o arrendamiento por un período no mayor al período fijado en los artículos para la duración de la sociedad o por un período menor de acuerdo a lo que requieran las circunstancias:

2. Realizar negocios con cualquier persona residente en Barbados;

3. Recibir depósitos de cualquier persona, contraviniendo la ley de Instituciones Financieras 1996-16.

B. Está prohibida cualquier invitación al público a suscribir cuotas o instrumentos.

Nombre	Dirección	Firma
LIZA A. HARRIDYAL-SODHA	#6 GUNSITE, BRITTONS HILL, ST. MICHAEL, BARBADOS	ILEGIBLE

BIOVAIL LABORATORIES INTERNATIONAL SRL

CERTIFICACIÓN

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
16 DIC. 2007
PABLO MENDEZ BARAJAS

Yo, ARLENE L. FONG, de Biovail Laboratories International SRL (La sociedad) de Chelston Park, Collymore Rock, St. Michael, Barbados por la presente declaro que soy gerente y secretario de la sociedad y que en mi calidad de tal, estoy autorizado para realizar esta declaración a nombre de la misma. Certifico que la sociedad es una sociedad legalmente constituida bajo las leyes de Barbados con el objeto de poseer y operar una empresa

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farmacéutica 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.

CERTIFICACIÓN NOTARIAL

Yo, GODFREY WINSTON HINDS, notario público para la isla de Barbados certifico que en la fecha y hora del presente compareció personalmente ante mí 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 entregó el mismo como un acto de su propia voluntad y libre albedrío y que ella presentó el certificado de constitución de Biovail Laboratories International SRL, que da fe de la afirmación anterior.

Expedido con mi firma y el sello notarial oficial hoy 5 de mayo de 2006.

FIRMA ILEGIBLE

NOTARIO PÚBLICO PARA LA ISLA DE BARBADOS

SELLO: REGISTRADOR SUPLENTE Y COMO TAL NOTARIO PÚBLICO PARA BARBADOS.

OFICINA DE PROPIEDAD INTELECTUAL Y ASUNTOS SOsocietarios.

APOSTILLA

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TUVE A LA VISTA
26 DIC 2007
ABEL MENDEZ BARAJAS
NOTARIO (E)

1. PAIS: BARBADOS

Este documento público

2. ha sido firmado por GODFREY WINSTON HINDS

3. quien actúa en su calidad de REGISTRADOR SUPLENTE ENCARGADO Y EN SU CALIDAD NOTARIO PÚBLICO PARA LA ISLA DE BARBADOS

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4. y lleva el sello/estampilla de NOTARIO PÚBLICO DE BARBADOS

CERTIFICADO

5. en BRIDGETOWN, BARBADOS 6. el 8 de mayo de 2006

7. por HUGHLAND ST CLAIR ALLMAN, JEFE DE PROTOCOLO ENCARGADO

8. Certificado número 657/2006

9. SELLO: MINISTERIO DE ASUNTOS EXTERIORES, BARBADOS

10. Firma: (ILEGIBLE)

COLO- 15366-706-001-3

WPCL002G ID 7834

Bogotá, 13 de junio de 2006.

Eduardo Calado Nogueira
TRADUCTOR OFICIAL
INGLES - ESPAÑOL INGLES
Res. 541 Febrero de 1974

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PAB[illegible]ASQUEZ BARAJAS
NOTARIO (E)

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) FIRMA(S) DE

Eduardo Calado

Noguera

COINCIDE(N) CON LA FIRMA REGISTRADA POR EL (LOS) EN ESTA NOTARIA

SANTAFE DE BOGOTA 14 JUN 2006

CODEX JURIS CIVILIS

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Notario Sexto Encargado

NO SE ASUME RESPONSABILIDAD SOBRE EL TEXTO

2006 [illegible] 12:32

JEFE DE LA OFICINA DE AUTORIZACIONES
BOGOTA D.C.

MINISTERIO DE RELACIONES EXTERIORES

Eduardo Calado
FIRMA AUTORIZADA
PARA EL CUMPLIMIENTO DE LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A LA VISTA

26 DIC 2007

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2007 (04.01.2007)

PCT

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WO 2007/002597 A2

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PCT/US2006/024832

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/693,906 27 June 2005 (27.06.2005) US

(71) Applicant: **BIOVAIL LABORATORIES INTERNATIONAL S.R.L.** [CA/CA]; 7150 Mississauga Road, Mississauga, Ontario L5N 8M5 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **OBEREGGER, Werner** [CA/CA]; 6653 Harlow Road, Mississauga, Ontario L5N 4T4 (CA). **ZHOU, Fang** [CA/US]; 5337 Sammie Kay Lane, Centreville, VA 20120 (US). **MAES, Paul** [BE/CA]; Toronto, Ontario (CA). **TURCHETTA, Stefano** [IT/IT]; Patricia (IT). **JACKSON, Graham** [IE/IE]; Dublin (IE). **MASSARDO, Pietro** [IT/IT]; Patricia (IT).

(74) Agents: **TESKIN, Robin, L.** et al.; HUNTON & WILLIAMS LLP, Intellectual Property Department, 1900 K Street, N.W., Suite 1200, Washington, DC 20006-1109 (US).

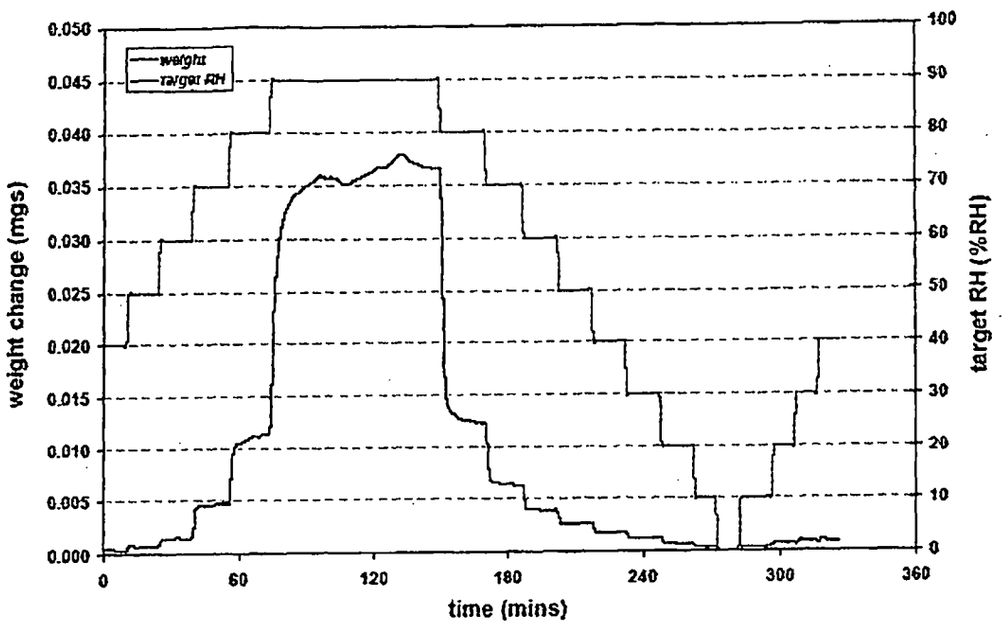
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: MODIFIED-RELEASE FORMULATIONS OF A BUPROPION SALT



(57) Abstract: The present invention relates to pharmaceutical compositions, formulations and medicaments comprising a bupropion salt, in particular, modified-release tablets comprising an effective amount of bupropion hydrobromide, and the use of the bupropion salt to prepare a medicament to treat a condition.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MODIFIED RELEASE FORMULATIONS OF A BUPROPION SALT

RELATED APPLICATIONS

[001] The present application claims priority from United States provisional application 60/693,906 filed June 27, 2005, the contents of which is incorporated by reference in their entirety.

FIELD OF THE INVENTION

[002] There is a need for dosage forms comprising a pharmaceutically acceptable salt of bupropion that is more stable than bupropion hydrochloride. Accordingly, the present invention relates to dosage forms comprising an effective amount of a pharmaceutically acceptable salt of bupropion that is more stable than bupropion hydrochloride. The present invention also relates to the use of such dosage forms for the treatment of one or more conditions in a subject suitable for treatment by bupropion or pharmaceutically acceptable salts thereof such as depression, nicotine addiction and obesity.

BACKGROUND

[003] Bupropion is an antidepressant chemically unrelated to tricyclics, tetracyclics, selective serotonin re-uptake inhibitors (SSRIs), or other known antidepressant agents. The drug resembles a psycho stimulant in terms of its neurochemical and behavioral profiles in vivo, but it does not reliably produce stimulant-like effects in humans at clinically prescribed doses. Its structure closely resembles that of diethylpropion and it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride and by its generic name amfebutamone hydrochloride. Bupropion hydrochloride is commercially available as an immediate release form (Wellbutrin®) and a sustained release form (Wellbutrin® SR and Zyban®). Both Wellbutrin® SR and Zyban® are chemically and pharmaceutically identical.

[004] The neurochemical mechanism of the antidepressant effect of bupropion is not well known. Bupropion does not inhibit monoamine oxidase. 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 experts believe that depression is caused by an imbalance among the amounts of neurotransmitters that are released.

It is believed that bupropion works by inhibiting the reuptake of the neurotransmitters dopamine, serotonin, and norepinephrine, an action which results in more dopamine, serotonin, and norepinephrine made available to transmit messages to other nerves. Accordingly, bupropion is unique in that its major effect is on dopamine, an effect which is not shared by the SSRIs (e.g. paroxetine (Paxil®), fluoxetine (Prozac®), sertraline (Zoloft®)) or the tricyclic antidepressants or TCAs (e.g. amitriptyline (Elavil®), imipramine (Tofranil®), desipramine (Norpramin®)).

[005] Wellbutrin® and Wellbutrin® SR are used for the management of depression. Zyban® has been approved as an aid to patients wanting to quit smoking. Wellbutrin®, the immediate release formulation of bupropion, is dosed three times a day, suitably with 6 or more hours in between doses. For patients requiring more than 300 mg bupropion a day, each dose should not exceed 150 mg. This requires administration of the 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 of the bupropion into the dissolution media in 45 minutes, and one of the major side effects of bupropion has been the incidence of seizures, which in part appears to be strongly associated with the immediate release of the bupropion into the system. Accordingly, sustained release products were developed to avoid the incidence of seizures. The sustained release products are dosed twice daily.

[006] In general, patient compliance is a problem with medications that require a multiple dosing regimen and is especially problematic with depressed individuals. While sustained release formulations have simplified the dosing regimen and increased patient compliance, there is still room for further simplifying the dosing regimen and further improving patient adherence to the dosing regimen. The development of an approved stable once daily modified-release bupropion formulation would be an advance in the art.

[007] The selection of a suitable salt for a drug candidate is recognized as an important step in the preclinical phase of drug development; however, the scientific literature on this topic is rather limited. Changing the salt form of a drug is a recognized means of modifying its chemical and biological properties without modifying its structure. As yet, there is no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity. 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 for the new pharmaceutical product.

[008] In general, a few of the factors that should be considered during a salt selection include: What is the effect of the salt on the chemical stability of the drug substance and the drug product? Does the salt form a hydrate? What is the solubility of the salt and is it appropriate for in vivo administration? What is the quality of the salt with regard to processing, issues with scale up, safety, etc.?

[009] According to the Chemical Abstracts Registry® Database, the only salts of bupropion that have been previously reported are the hydrochloride (HCl), (2Z)-2-butenedioate, (2E)-2-butenedioate, methane sulfonate, formic acid, 2-hydroxy-1,2,3-propanetricarboxylate, phosphate and trifluoromethanesulfonate salts.

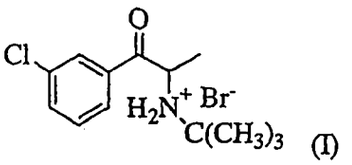
[010] There is a need for a once daily formulation of a pharmaceutically acceptable salt of bupropion with enhanced stability.

SUMMARY

[011] The present invention relates to dosage forms comprising an effective amount of a pharmaceutically acceptable salt of bupropion (bupropion hydrobromide) which is more stable than bupropion hydrochloride. In particular such bupropion compositions are more stable than otherwise equivalent bupropion hydrochloride compositions when stored for at least 3 months and/or at least 6 months at 40 degrees C and 75% relative humidity ("accelerated storage conditions") as evidenced by a reduced amount of at least one moiety characteristic of bupropion degradation and/or exhibit less fluctuation or reduction in potency after being stored for at least 3 months and/or at least 6 months under accelerated storage conditions relative to an otherwise similar bupropion hydrochloride composition as evidenced e.g., by less fluctuation in the in vitro dissolution profile in at least one dissolution medium over a 24 hour period.

[012] The present invention also relates to the use of such more stable bupropion hydrobromide dosage forms for the treatment of one or more conditions in a subject.

[013] The dosage forms of the present invention comprise a compound of formula I (bupropion hydrobromide):



(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.

[014] In other embodiments of the present invention, the bupropion salt can be in the form of its anhydrous, hydrated, and solvated forms, in the form of prodrugs, and in the individually optically active enantiomers of the bupropion salt, such as for examle (+)-bupropion and (-)-bupropion. Suitable pharmaceutically acceptable salts of bupropion for use in the present invention are more stable than bupropion hydrochloride. 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.

[015] Another embodiment of the present invention contemplates the use of bupropion hydrobromide to prepare a medicament to treat a condition which can benefit from administration of bupropion, wherein said medicament has greater stability than a corresponding medicament comprising bupropion hydrochloride. Herein enhanced stability means that the salt or a composition containing is more stable after being stored for at least 3 months and/or 6 months at 40 degrees C and 75 % relative humidity (accelerated storage conditions) as evidenced by a lesser amount of at least one moiety characteristic of bupropion degradation and/or a reduction or fluctuation in potency evidenced e.g., by a greater fluctuation in the in vitro dissolution profile over at least a 12 or a 24 hour period in at least one dissolution medium relative and under the same conditions to an otherwise equivalent bupropion hydrobromide compostion stored for the same length of time under the same accelerated storage conditions.

[016] As discussed infra and generally known in the art appropriate dissolution medium and appropropriate 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 Pharmacopoiea and its Eoropean 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 bufffer pH 1.5; Acetate buffer pH 4.5; Phosphate Buffer pH 6.5; or Phosphate Buffer pH 7.4 at 75 RPM at 37 degrees C +/- 0.5 degrees C.

[017] Additionally, other disolution media include USP-3 media and USP-3 dissolution conditions i.e., SGF pH 1.2; Acetate buffer pH 4.5 and Phosphate Buffer pH 6.8.

[018] In another embodiment of the present invention, the dosage forms comprising bupropion hydrobromide can be used to treat a condition which can benefit from administration of bupropion such as depression, seasonal effective disorder, smoking cessation or obesity.

[019] Another embodiment of the present invention contemplates the use of bupropion hydrobromide to prepare a modified-release tablet of bupropion hydrobromide with enhanced stability. The tablets of the present invention, comprising bupropion hydrobromide, have unexpected enhanced stability compared to the prior art bupropion hydrochloride tablets.

[020] In another embodiment the present invention contemplates the use of bupropion hydrobromide to produce once-daily administrable tablets or other dosage forms that are bioequivalent to Welbutrin™ or Zyban/Wellbutrin™ SR tablets as defined by FDA criteria when administered once daily to a subject in need thereof. In particular at least one of the Tmax, Cmax, and AUC profile are within 80-125% of Wellbutrin™- and Zyban™/Wellbutrin™ when administerd once daily to a subject in need thereof. Preferably, these formulatuions also will be free of any significant food effect.

[021] In addition the present invention provides bupropion hydrobromide dosage forms containing at least one coating, e.g., tablets, which are resistant to dose dumping in high alcohol, e.g., 40% ethanol, because of the presence of an appropriate coating, i.e., a SmartCoat.™

[022] Another embodiment of the present invention further contemplates a method of preparing a medicament for the treatment of a condition which can benefit from the administration of bupropion comprising bringing an effective amount of bupropion hydrobromide into contact with one or more pharmaceutically acceptable carriers, diluents and/or excipients.

[023] Another embodiment of the present invention contemplates a method of treating a condition which can benefit from the administration of bupropion comprising administering an effective amount of bupropion hydrobromide to a subject. For example, such conditions which can benefit from administration of bupropion hydrobromide include but are not limited to depression, including seasonal effective disorder, cognitive symptoms in depression, bipolar depression, post partum depression, minor depression, lack of energy in depression, suicidal

depression, 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/hyperactiviy disorder (ADHD), narcolepsy, hypersomnia, substance-abuse disorders, stimulant dependence, marijuana dependence, nicotine dependence, obesity, female and male sexual dysfunction such as premature ejaculation, premenstrual syndrome, premenstrual dysphoric disorder, neuropathic pain, fibromyalgia, diabetic neuropathy, viral infection, sleep apnea, sleep disorders and migraines. The conditions may be focused on different demographic populations, such as reproductive related mood disorders, specific age population disorders and specific ethnic population disorders.

[024] According to an aspect of the invention, there is provided a composition for administration to a subject in need of treatment for a condition. The composition comprises a pharmaceutically effective amount of a bupropion salt that is more stable than bupropion hydrochloride as defined herein. In addition, the composition is more stable than a corresponding composition comprising bupropion hydrochloride.

[025] The present invention includes both oral and non-oral bupropion hydrobromide containing medicaments. Prior to the present invention medicaments containing bupropion hydrobromide were unavailabe Particularly, the invention embraces compositions suitable for topical, injectable, inhalation and other modes of administration. Typically the medicaments of the present invention are orally administrable.

[026] In particular the invention includes extended release formulations. In another aspect,, the present invention includes delayed release formulations. Further, the present invention embraces enhanced absorption formulations.

[027] In a particular embodiment, the inventive compositions include controlled release matrix tablet formulations.

[028] In a more particular implementation of the invention, a bupropion medicament composition according to the invention may comprise (i) a core that includes bupropion hydrobromide, a binder and a lubricant; and (ii) a control releasing coat substantially surrounding said core; wherein said composition provides controlled release of said bupropion hydrobromide. Such composition optionally may comprise one or more additional coatings surrounding the core and/or the control releasing coat such as moisture barrier coats, enteric coats or coatings that affect the physical integrity and/or appearance of the bupropion 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 control releasing coat can include a water-insoluble polymer, a water-soluble polymer, and optionally a plasticizer. The water-insoluble polymer can be selected from a range of water insoluble polymers useful in extended release pharmaceutical compositions such as ethylcellulose. The water-soluble polymer can be selected from a variety of water-soluble polymers useful in extended release pharmaceutical compositions such as polyvinylpyrrolidone. The plasticizer if present can be selected from a range of known plasticizers such as mixtures of polyethylene glycol 4000 and dibutyl sebacate. These compositions include once-daily administrable compositions that are bioequivalent to Wellbutrin™ or Zyban™/Wellbutrin™ SR tablets when administered once-daily to a subject in need thereof.may be bioequivalent. These compositions optionally may not exhibit a food effect and/or may be resistan to dose dumping in the prersence of high alcohol concentrations (i.e., 40% by weight of ethanol).

[029] In a more particular implementation of the invention , the subject bupropion composition comprises (i) a core that includes bupropion hydrobromide, a binder and a lubricant; and (ii) a control releasing coat substantially surrounding said core; wherein said control releasing 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 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 of the polyglycol. Optionally, this medicament may comprise one or more additional coatings surrounding the core and/or control-release coating such as moisture barrier coats, enteric coats, coats that preclude dose dumping in specific media such as alcohol, and coatings that affect the physical stability or integrity of the medicament and/or its physical appearance.

[030] In a particular implementation of the invention, the subject bupropion composition comprises multiparticulates.

[031] In a particular implementation of the invention, the subject bupropion composition comprises a second drug. The second drug can be any drug which may be administered in combination with the subject bupropion salt such as other anti-depressants, SSRI's, anti-anxiety agents, etc. The invention embraces drug combinations wherein the second drug may elicit a synergistic benefit on bupropion efficacy as well as non-synergistic drug combinations. In

particular the invention embraces bupropion hydrobromide compositions wherein the second drug is citalopram, escitalopram and/or venlafaxine.

[032] According to another aspect of the invention, there is provided a method of using a composition according to any of the foregoing claims for treatment in a subject in need of such administration. This includes in particular the treatment of depression, obesity and abuse disorders such as nicotine addiction and smoking cessation. In an exemplary embodiments such treatments comprise once-daily dosage regimens.

[033] According to another aspect of the invention, there is provided a use of bupropion hydrobromide to prepare a medicament to treat conditions which benefit from administration of bupropion, wherein said medicament has greater stability than a corresponding medicament comprising bupropion hydrochloride.

[034] In accordance with one aspect of the present invention, there is provided a controlled release tablet, comprising (i) a core comprising an effective amount of a bupropion hydrobromide, a binder, a lubricant; and (ii) a control-releasing coat surrounding said core; and optionally (iii) a moisture barrier surrounding said control-releasing coat or the core; and; wherein the extended release tablet exhibits a dissolution profile such that after 2 hours, no more than 20% of the bupropion hydrobromide content is released, for example in certain embodiments 2% to 18%, 4% to 8%, or 5% of the bupropion hydrobromide content is released after 2 hours; after 4 hours, 15% to 45% of the bupropion hydrobromide content is released, for example in certain embodiments 21% to 37%, 28% to 34%, or 32% of the bupropion hydrobromide content is released after 4 hours; after 8 hours, 40% to 90% of the bupropion hydrobromide content is released, for example in certain embodiments 60% to 85%, 68% to 74%, or 74% of the bupropion hydrobromide content is released after 8 hours; and after 16 hours no less than 80% of the bupropion hydrobromide content is released, for example in certain embodiments not less than 93%, not less than 96%, or not less than 99% of the bupropion hydrobromide content is released after 16 hours; and wherein the bupropion hydrobromide salt contained insaid extended release tablet has greater stability than a tablet having the same composition with the exception that bupropion hydrobromide is replaced with bupropion hydrochloride.

[035] In another aspect the composition exhibits a dissolution profile such that after 2 hours not more than 40% of the bupropion hydrobromide is released, e.g., 33%, after 4 hours from 40-

75%, e.g., 59% of the bupropion hydrobromide is released, after 8 hours not less than 75% of the bupropion hydrobromide is released, e.g., 91%, and after 16 hours not less than 85% of the bupropion hydrobromide is released, e.g., 97%. These medicaments will typically comprise 50-500 mg of bupropion hydrobromide. In exemplary embodiments diosclosed herein the medicament contain 174 mg or 348 mg of bupropion hydrobromide.

[036] In accordance with another aspect of the present invention, there is provided an enhanced-absorption tablet, comprising (i) a core comprising an effective amount of bupropion hydrobromide, a binder, a lubricant; and (ii) a control-releasing coat surrounding said core; and wherein the enhanced absorption tablet exhibits a dissolution profile such that after 2 hours, no more than 25% of the bupropion hydrobromide content is released, for example in certain embodiments 10% to 20% of the bupropion hydrobromide content is released after 2 hours; after 4 hours, 25% to 55% of the bupropion hydrobromide content is released, for example in certain embodiments 30% to 50%, of the bupropion hydrobromide content is released after 4 hours; after 8 hours, more than 60% of the bupropion hydrobromide content is released, for example in certain embodiments 70% to 90% of the bupropion hydrobromide content is released after 8 hours; and after 16 hours more than 70% of the bupropion hydrobromide content is released, for example in certain embodiments more than 80% of the bupropion hydrobromide content is released after 16 hours; and wherein said extended release tablet has greater stability than a tablet having the same composition with the exception that bupropion hydrobromide is replaced with bupropion hydrochloride. This composition optionally may further comprise one or more additional coats surrounding the core and/or control-release coat.

[037] In an exemplary embodiment this composition may comprise a dissolution profile such that after 2 hours not more than 40% of bupropion hydrobromide is released therefrom, e.g., 33%; after 4 hours 40-75% of bupropion hydrobromide is released therefreom, e.g., 59%, after 8 hours not less than 75% of bupropion hydrobromide is released therefrom, e.g., 91%, and after 16 hours not less than 85% of bupropion hydrobromide is released therefrom, e.g., 97%.

[038] In accordance with a further aspect of the invention there is provided a salt of bupropion and polymorphic forms thereof having enhanced stability wherein the salt is hydrobromide, and wherein enhanced stability refers to the reduced formation of at least one degradation product characteristic of bupropion degradation and/or the increased retention of potency as evidenced e.g., by a reduced fluctuation in the in vitro dissolution profile in at least one dissolution medium

relative to an otherwise equivalent formulation containing bupropion hydrochloridewhen the formulations containing these bupropion salts are stored for prolonged time periods under equivalent conditions. In particular enhanced stability referes to bupropion hydrobromide compositions that are less subject to degradation than an otherwise equivalent bupropion hydrochloride composition when stored under accelerated storage conditions, i.e., 40 degrees C at 75% relative humidity for at least 3 months, and/or for at least 6 months or longer and/or which exhibits less fluctuation or reduction in potency as evidence by a reduced fluctuation in the in vitro dissolution profile in at least one dissolution medium wherein dissolution is effected under the same conditions after the bupropion hydrobromide and bupropion hydrochloride compositions are stored for at least 3 months and/or at least 6 months at 40 degrees C and 75% relative humidity. In the present invention, as described infra, degradation is assayed based on the amount of at least one compound characteristic of bupropion degration.

[039] More particularly, the present invention embraces enhancede absorption tablets comprising (i) a core comprising an effective amount of bupropion HBr, a binder, a lubricant: and (ii) a control-releasing coat surrounding said core; wherein the enhanced absorption tablet exhibits a dissolution profile such that after 2 hours no more than 40% bupropion is released, (e.g, 33%); after 4 hours 40-75% bupropion is released (e.g., 59%), after 8 hours at least 75% is released (e.g., 91%); and after 16 hours at least 85% is released (e.g, 97%)

[040] As discussed infra, in vitro dissolution of bupropion from controlled or extended release formulations according to the invention can be determined by methods well known to those skilled in the pharmaceutical art. Suitable methods are contained in the United States Pharmacopoiea (USP) as well as European and Japanese counterpats of the USP and are exemplified infra. This includes by way of example effecting dissolution in a USP 1 apparatus (Rotating Type Basket Method) in 900 ml water, 0.1N HCl, 0.1N HCl + 0.1% Cetrimide, USP Buffer pH 1.5, Acetate Buffer pH 6.5 or Phosphate Buffer pH 7.4 at 75 RPM at 37 degrees C +/- 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[041] Figure 1 shows a DVS profile for bupropion hydrobromide (HBr).

[042] Figure 2 shows DVS isotherm data for bupropion HBr.

[043] Figure 3 is a bar graph showing the results of stability testing on the bupropion salts mixed with excipients in closed vials over 20 days at 40°C/75% relative humidity (RH).

[044] Figure 4 is a bar graph showing the potency of the bupropion salts mixed with excipients after storage in closed vials over 20 days at 40°C/75%RH compared to their initial potency.

[045] Figure 5 is a bar graph showing the potency of the bupropion salts mixed with excipients and water after storage in closed vials over 32 days at 40°C compared to their initial potency.

[046] Figure 6 is a bar graph showing the potency of the bupropion salts mixed with excipients, water, isopropyl alcohol and ethanol after storage in closed vials over 32 days at 40°C compared to their initial potency.

[047] Figure 7 is a bar graph showing the potency of the bupropion salts mixed with excipients, isopropyl alcohol and ethanol after storage in closed vials over 32 days at 40°C compared to their initial potency.

[048] Figure 8 is a bar graph showing the % impurities for the bupropion salts mixed with excipients and treated for 32 days in closed vials and spiked with water.

[049] Figure 9 is a bar graph showing the % impurities for the bupropion salts mixed with excipients and treated for 32 days in closed vials ans spiked with water, isopropyl alcohol (IPA) and ethanol (EtOH).

[050] Figure 10 is a bar graph showing the % impurities for the bupropion salts mixed with excipients and treated for 32 days in closed vials and spiked with isopropyl alcohol (IPA) and ethanol (EtOH).

[051] Figure 11 is a flow chart showing the overall process for the development of bupropion HBr XL tablets.

[052] Figure 12 is a flow chart demonstrating the granulation process of the bupropion HBr XL and EA tablets.

[053] Figure 13 is a flow chart showing the overall tabletting process of bupropion HBr XL.

[054] Figure 14 is a flow chart showing the overall coating process of bupropion HBr XL.

[055] Figure 15 is a dissolution profile of the 4kp, 6-7kp and 9-10kp tablets, comparing the effects of hardness on dissolution in the study on Batch BUP-HBr-XL-009-5.

[056] Figure 16 is a dissolution profile of the 348mg Bupropion HBr cores which have been compressed using 9mm tooling in the study on Batch BUP-HBr-XL-009-5.

[057] Figure 17 is a dissolution profile of the 348mg Bupropion HBr cores which have been compressed using 10mm tooling in the study on Batch BUP-HBr-XL-009-5.

[058] Figure 18 is a dissolution profile comparison of the 9mm and 10mm diameter 348mg Bupropion HBr cores in the study on Batch BUP-HBr-XL-009-5.

[059] Figure 19 is a dissolution profile of the 174mg in the study on Batch BUP-HBr-XL-021-5.

[060] Figure 20 is a dissolution profile of BUP-HBr-XL-348mg-013-5 (28mg, 30mg, 32mg and 34 mg weight gains).

[061] Figure 21 is a dissolution profile of BUP-HBr-XL-348mg-013-5 (5mg, 6mg, and 7mg weight gains).

[062] Figure 22 is a dissolution profile of BUP-HBr-XL-348mg-018-5 (26mg, 28mg, 30mg and 32 mg weight gains).

[063] Figure 23 is a dissolution profile of BUP-HBr-XL-348mg-018-5 (7mg weight gain).

[064] Figure 24 is a dissolution profile of BUP-HBr-XL-174mg-022-5 (22mg, 24mg, 28mg and 30 mg weight gains).

[065] Figure 25 is a dissolution profile of BUP-HBr-XL-174mg-022-5 (5mg, 6mg, and 7mg weight gains).

[066] Figure 26 is a dissolution profile of BUP-HBr-XL-348mg-023-5 (26mg, 28mg, 30mg and 32mg weight gains).

[067] Figure 27 is a dissolution profile of BUP-HBr-XL-348mg-025-5 (26mg, 28mg, 30mg, and 32mg mg weight gains).

[068] Figure 28 is a dissolution profile of BUP-HBr-XL-348mg-025-5 (5mg, 6mg, and 7mg weight gains).

[069] Figure 29 is a dissolution profile of BUP-HBr-XL-348mg-026-5 (26mg, 28mg, 30mg, and 32mg weight gains).

[070] Figure 30 is a dissolution profile of BUP-HBr-XL-174mg-027-5 (22mg, 24mg, and 26mg weight gains).

[071] Figure 31 is a dissolution profile of BUP-HBr-XL-174mg-027-5 (4mg, 5mg, 6mg, and 7mg weight gains).

[072] Figure 32 is a flow chart showing the overall process for the development of bupropion HBr EA tablets.

[073] Figure 33 is a flow chart demonstrating the granulation process of the bupropion HBr EA tablets.

[074] Figure 34 is a flow chart showing the compression process of the 300 mg and 150 mg bupropion HBr EA Tablets.

[075] Figure 35 is a flow chart showing the coating process of 150 mg and 300 mg bupropion HBr EA Tablets with an Ethocel ™ Coating.

[076] Figure 36 is a dissolution profile of the of tablet cores at different hardness levels (4kp, 6-7kp and 9kp) in the study on Batch BUP-HBr-XL-016-5.

[077] Figure 37 is a dissolution profile of the 300mg Bupropion HBr EACores in the study on Batch BUP-HBr-XL-016-5.

[078] Figure 38 is a dissolution profile of the 150mg Bupropion HBr Cores in the study on Batch BUP-HBr-XL-016-5.

[079] Figure 39 is a dissolution profile of BUP-HBr-EA-300mg-001-5 (44mg, 46mg, 48mg, 50mg 52mg, and 54mg weight gains).

[080] Figure 40 is a comparative USP3 dissolution profile of Bupropion HBr 300mg EA Tablets with 52mg weight gain to the in vivo and the in vitro profiles of the target (Bupropion HCl 300mg).

[081] Figure 41 is a dissolution profile of BUP-HBr-EA-150mg-002-5 (18mg, 20mg, 22mg, 24mg, 26mg, 28mg, 30mg, 32mg, 34mg and 36mg weight gains).

[082] Figure 42 is a dissolution profile of BUP-HBr-EA-300mg-003-5 (44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains).

[083] Figure 43 is a dissolution profile of BUP-HBr-EA-300mg-004-5 (44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains).

[084] Figure 44 is a dissolution profile of BUP-HBr-EA-300mg-005-5 (44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains).

[085] Figure 45 is a dissolution profile of BUP-HBr-EA-150mg-006-5 (24mg, 28mg, 32mg, 34mg and 36mg weight gains).

[086] Figure 46 is a comparative USP3 dissolution profile of bupropion HBr 150mg EA Tablets with 24 and 34mg weight gains to the in vivo and the in vitro profiles of the target (bupropion HCl 300mg).

[087] Figure 47 is a bar graph showing the % impurities for the bupropion HCl XL 300mg and bupropion HBr 348mg EC coated tablets at 40°C and 75% relative humidity.

[088] Figure 48 is a bar graph showing the % impurities for the bupropion HCl 300mg (Wellbutrin XL) and bupropion HBr 348mg XL final tablets at 40°C and 75% relative humidity.

[089] Figure 49 contains bar graphs showing the % of 3-CBA formed in forced degradation studies of bupropion hydrochloride (HCl) vs. bupropion HBr in the presence of excipients.

[090] Figure 50 contains bar graphs showing the % of 852U77 formed in forced degradation studies of bupropion HCl vs. bupropion HBr in the presence of excipients.

[091] Figure 51 contains bar graphs showing the % of 20U78 formed in forced degradation studies of bupropion HCl vs. bupropion HBr in the presence of excipients.

[092] Figure 52 contains bar graphs showing the % of 827U76 formed in forced degradation studies of bupropion HCl vs. bupropion HBr in the presence of excipients.

[093] Figure 53 is a graph showing the loss of API in a thermal gravimetric analysis (TGA) experiment at 100 °C of bupropion HCl vs. bupropion HBr.

[094] Figure 54 is a graph showing the relative powder X-ray diffraction (PXRD) for bupropion hydrobromide polymorphic form I.

[095] Figure 55 is a graph showing the differential scanning calorimetry (DSC) profile of bupropion hydrobromide polymorphic form I.

[096] Figure 56 is a graph showing the relative PXRD for bupropion hydrobromide polymorphic form II.

[097] Figure 57 is a graph showing the DSC profile of bupropion hydrobromide polymorphic form II.

[098] Figure 58 is a graph showing the relative PXRD for bupropion hydrobromide polymorphic form III.

[099] Figure 59 is a graph showing the DSC profile of bupropion hydrobromide polymorphic form III.

[0100] Figure 60 is a graph of the relative PXRD of a sample of bupropion hydrobromide polymorphic form I after 6 months under the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) conditions (40 °C, 75%R.H.).

[0101] Figure 61 is a graph of the PXRD of a sample of bupropion hydrobromide polymorphic form II after 1 month under ICH conditions (40 °C, 75%R.H.).

[0102] Figure 62 is a graph of the PXRD of a sample of bupropion hydrobromide polymorphic form III after 1 month under ICH conditions (40 °C, 75%R.H.).

[0103] Figure 63 contains the results of stability studies for Bupropion HBr XL 174 mg core (Lot # Bup-HBr-XL-004-5 core; Bupropion HBr XL 348 mg core (Lot # Bup-HBr-XL-009-5 core; Bupropion HCl XL 150 mg core (Lot # 05E056) and Bupropion HCl XL 300 mg core (Lot # 05D380) initially, after 10 days open and closed, and after 20 days open and closed. The % of impurities 3-CBZ, 852U77, 20U78dilu, 827U76 are shown therein.

[0104] Figure 64 and Figure 65 respectively contain stability data for bupropion 348 mg HBr XL tablets (Lot # Bup-HBr-XL-348-025-5) and Bupropion HBr EA 300 mg tablets (Lot # Bup-HBr-EA-300-001-5 initially and after 3 months, 6 months, 9 months and 12 months under accelerated storage conditions (40 degrees C and 75% relative humidity). The assay tested for amount of impurities 3-CBA, 852U77, 20U78/diluent, 827U76, and also compared the dissolution profiles and appearance thereof.

[0105] Figure 66 compares the dissolution profiles and in vitro drug release of Bupropion HBr XL 348 mg tablets (final) Lot # Bup-HBr-XL-012-5, Wellbutrin XL 300 mg tablets final (Lot # 05A116), Bupropion HBr XL 348 mg tablets ECl) Lot # Bup-HBr-XL-012-5 (EC 32mg wg), and Wellbutrin XL 300 mg tablets (ECl) (Lot # 05D047) in different USP-3 media (SGF pH 1.2, Acetate Buffer pH 4.5, and Phosphate Buffer pH 6.8 over a period of 16 hours.

[0106] Figure 67 compares the dissolution profiles and drug release for Bupropion HBr 348 mg Lot # 05E304 in different USP-3 media (SGF pH 1.2, Acetate Buffer pH 4.5, Phosphate Buffer SIF pH 6.8) over a period of 16 hours and further compares this release profile against the release profile for Bup 300 XL Target (01L238) in vivo and BUP 300XL Target (01L238) in vitro in USP-3 media.

[0107] Figure 68 contains comparative dissolution profiles for Bupropion HBr XL 348 mg and Wellbutrin XL (final and EC) in USP-3 media (pH 1.2 SGF, pH 4.5 acetate buffer and pH 6.8 phosphate buffer over a period of 16 hours.

DEFINITIONS

[0108] The term "bupropion salt" herein has its ordinary meaning and includes any salt of bupropion.

[0109] The term "buropion salt that is more stable than bupropion hydrochloride"refers to a bupropion salt or a composition containing that is less subject to degradation than an otherwise equivalent bupropion hydrochloride salt or composition containing when stored for at least 3 months, 4 months, 5 months, and/or at least 6 months under accelerated storage conditions (40 degrees C, and 75% relative humidity), and/or when stored for at least 3, 4, 5 and/or 6 months under accelerated storage conditions (40 degrees C and 75% relative humidity) and/or which exhibits less of a reduction or fluctuation in potency as eviddenced by less fluctuation in the in vitro dissolution profile in at least one dissolution medium relative to an otherwise similar bupropion hydrochloride composition wherein dissolution is effected under the same conditions after these compositions are stored for at least 3, 4, 5, or 6 months at 40 degrees C at 75% relative humidity. Particularly, bupropion hydrobromide salts and polymorphs thereof may result in bupropion formuulations that exhibit dissolution profiles over time that are less subject to fluctuation when stored under accelerated storage conditions for prolonged time periods, i.e., at least 3 , 4, 5, or 6 months at 40 degrees C and 75% relative humidity.

[0110] The term "active", "active agent", "active pharmaceutical agent", "active drug" or "drug" as used herein means any active pharmaceutical ingredient ("API"), including its pharmaceutically acceptable salts (e.g. the hydrochloride salts, the hydrobromide salts, the hydroiodide salts, and the saccharinate salts), as well as in the anhydrous, hydrated, and solvated forms, in the form of prodrugs, and in the individually optically active enantiomers of the API as well as polymorphs of the API.

[0111] The term "dose dumping" herein refers to the rapid release of a drug from a medicament under certain conditions such as solvent conditions e.g., high (40%) ethanol.

[0112] The term "other drug" or "second drug" as used herein means a drug other than bupropion, including but not limited to anti-depression agents, other neuropsychiatric drugs, vasodilators, anti-anxiety agents, appetite modulators, sleep modulating drugs, SSRIs, anti-viral agents, anti-pain agents, anti-migraine agents, anti-inflammatories (both steroidal and non-steroidal) and more particularly may include citalopram, escitalopram, venlafaxine, clozapine, melperone, amperozide, iloperidone, risperidone, quetiapene, olanzapine, ziprasidone, aripiprazole, reboxetine, Viagra®, sertraline, paroxetine, fluoxetine, gabapentin, valproic acid,

amitriptyline, lofepramine, fluvoxamine, imipramine, mirtazapine, nefazodone, nortriptyline, SAM-E, 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 in the anhydrous, hydrated, and solvated forms, in the form of prodrugs, and in the individually optically active enantiomers of the drug.

[0113] The term "formulation" or "composition" as used herein refers to the drug in combination with pharmaceutically acceptable carriers and additional inert ingredients. This includes orally administrable formulations as well as formulations administrable by other means.

[0114] The term "dosage form" as used herein is defined to mean a pharmaceutical preparation in which doses of active drug are included.

[0115] "Modified release dosage forms" as used herein is as defined by the United States Pharmacopoeia (USP) as those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional, immediate release or uncoated normal matrix dosage forms. The rate of release of the active drug from a modified release dosage form is controlled by features of the 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 the invention can be contrasted to conventional, immediate release, or uncoated normal matrix dosage forms which typically produce large maximum/minimum plasma drug concentrations (Cmax/Cmin) due to rapid absorption of the drug into the body (i.e., in vivo, relative to the drug's therapeutic index; i.e., the ratio of the maximum drug concentration needed to produce and maintain a desirable pharmacological response). In conventional, immediate release or uncoated normal matrix dosage forms, the drug content is released into the gastrointestinal tract within a short period of time, and plasma drug levels peak shortly after dosing. The design of conventional, immediate release or uncoated normal matrix 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 the invention, on the other hand, improve the therapeutic value of the active drug by reducing the ratio of the maximum/minimum plasma drug concentration (Cmax/Cmin) while maintaining drug plasma levels within the therapeutic window. The modified release dosage forms of the invention attempt to deliver therapeutically effective amount of bupropion salt and combinations thereof as a once-daily dose 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 a therapeutic benefit over a 24-hour period. The modified release dosage forms of the 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 of the bupropion salt which remains substantially constant within the therapeutic range of bupropion salt for at least a 24-hour period. Alternatively, modified-release dosage forms can be designed to provide a quick increase in the plasma concentration of the bupropion salt, which although may not remain constant, declines at rate such that the plasma concentration remains within the therapeutic range for at least a 12 hour and desirably at least a 24-hour period.

[0116] The modified release dosage forms of the 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, "modified release matrix dosage forms", "normal release matrix dosage forms" coated with at least one "control-releasing coat", "osmotic dosage forms", "multiparticulate dosage forms", and "gastric retention dosage forms". 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", "prolonged-release", and "sustained-release" are used interchangeably herein. For the discussion herein, the definition of the term "modified-release" encompasses the scope of the definitions for the terms "extended release", "enhanced-absorption", "controlled release", and "delayed release".

[0117] "Controlled release dosage forms" or "control-releasing dosage forms", or dosage forms which exhibit a "controlled release" of the bupropion salt as used herein is defined to mean dosage forms administered once-or twice-daily that release the bupropion salt at a controlled rate and provide plasma concentrations of the bupropion salt that remain controlled with time within the therapeutic range of the bupropion salt over a 12 or 24-hour period. "Controlled release" or "control releasing" is defined to mean release of the drug gradually or in a controlled manner per unit time. For example, the controlled rate can be a constant rate providing plasma concentrations of the bupropion salt that remain invariant with time within the therapeutic range of the bupropion salt over at least a 12 or 24-hour period.

[0118] "Sustained-release dosage forms" or dosage forms which exhibit a "sustained-release" of the bupropion salt as used herein is defined to mean dosage forms administered once-daily that provide a release of the bupropion salt sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period of time such that the sustained-release dosage form provides therapeutic benefit over a 12 or 24-hour period.

[0119] "Extended-or sustained-release dosage forms" or dosage forms which exhibit an "extended or sustained release" of the bupropion salt as used herein is defined to include dosage forms administered once-or twice-daily that release the bupropion salt slowly, so that plasma concentrations of the bupropion salt are maintained at a therapeutic level for an extended period of time such that the extended or sustained-release dosage form provides therapeutic benefit over a 12 or 24-hour period.

[0120] "Prolonged-release dosage forms" or dosage forms which exhibit a "prolonged release" of the bupropion salt as used herein is defined to mean dosage forms administered once daily which provide for absorption of the bupropion salt over a longer period of time than from a conventional, immediate release or uncoated normal release matrix dosage form and which provide therapeutic benefit over at least a 12 hour and more typically at least a 24-hour period.

[0121] "Delayed-release dosage forms" or dosage forms which exhibit a "delayed release" of the bupropion salt as used herein is defined to mean dosage forms administered 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" which represents latency, that is, the time required for the drug to reach minimum effective concentration.

[0122] "Enhanced absorption dosage forms" or dosage forms which exhibit an "enhanced absorption" of the bupropion salt as used herein is defined to mean dosage forms that when exposed to like conditions, will show higher release and/or more aborption of the burpopion 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.

[0123] The term "controlled release matrix" as used herein is defined to mean a dosage form in which the bupropion salt and combinations thereof is dispersed within a matrix, which matrix

can be either insoluble, soluble, or a combination thereof. Controlled release matrix dosage forms of the insoluble type are also 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 of the soluble type are also referred to as "hydrophilic colloid matrices", "erodible matrices", or "reservoir systems". Controlled release matrix dosage forms of the invention refer to dosage forms comprising an insoluble matrix, a soluble matrix or a combination of insoluble and soluble matrices in which the rate of release 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 coat" to further slow the release of the bupropion salt from the controlled release matrix dosage form. Such coated controlled release matrix dosage forms can exhibit "modified-release", controlled-release", "sustained-release", "extended-release", "prolonged-release", "delayed-release" or combinations thereof of the bupropion salt.

[0124] The term "normal release matrix" as used herein is defined to mean dosage forms in which the bupropion salt and combinations thereof is dispersed within a matrix, which matrix can be either insoluble, soluble, or combinations thereof but constructed such that the release of the bupropion salt mimics the release rate of an uncoated non-matrix conventional or immediate release dosage form comprising the bupropion salt. The release rate from normal release matrix dosage forms can be slowed down or modified in conjunction with a "control releasing coat".

[0125] A "control releasing coat" or "controlled release coat" as used herein is defined to mean a functional coat which can for example comprise at least one pH independent polymer, pH dependent (such as for example enteric or reverse enteric types) polymer, soluble polymer, insoluble polymer, lipids, lipidic materials or combinations thereof which when applied onto a dosage form can slow (for example when applied to a normal release matrix dosage form), further slow (for example when applied to a controlled release matrix dosage form) or modify the rate of release of the bupropion salt when applied to an uncoated dosage form. For example, the control releasing coat can be designed such that when the control releasing coat is applied to a dosage form, the dosage form in conjunction with the control releasing coat can exhibit the release of the bupropion salt, such as for example, as a "modified-release", "controlled-release", "sustained-release", "extended-release", "delayed-release", "prolonged-release" or combinations

thereof. The "control releasing coat" can optionally comprise additional materials that can alter the functionality of the control releasing coat.

[0126] The term "moisture barrier" as used herein is one, which impedes or retards the absorption of moisture. It is known that bupropion salts are hygroscopic and, as such, are susceptible to decomposition over time under high humidity conditions. The proportion of the components of the moisture barrier and the amount of the moisture barrier optionally applied onto the control-releasing coat or onto the core is typically 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 enhancer. The permeation enhancer is a hydrophilic substance, which allows water to enter without physical disruption of the coating. The moisture barrier may additionally contain other conventional inert excipients, which may improve processing of the extended-release formulation described herein.

[0127] The term "medicament" as used herein refers to all possible 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, suspensions, topicals such as transdermal and transmucoasal compositions and delivery systems (containing or not containing matrices), injectables, and inhalable compositions.

[0128] The term "enhanced stability", "greater stability", "increased stability" or "more stable" as used herein when referring to a bupropion salt (bupropion HBr) means that the bupropion salt (bupropion hydrobromide), and compositions, formulations or medicaments comprising the bupropion salt, when exposed to like conditions, i.e, when stored for at least 3 months under accelerated storage conditions (40 degrees C, 75% relative humidity) and/or when stored for at least 3,4,5 and/or 6 months or a year or more under accelerated storage conditions (40 degrees C, 75% relative humidity) show less degradation as determined by the formation of less of at least one degradation product than an otherwise similar composition containing bupropion HCl.. Additionally enhanced stability or greater stability or increased stability of a bupropion salt (relative to bupropion HCl) includes bupropion HBr compositions which exhibit more consistent

dissolution profiles and therefore potency, compared to an otherwise similar bupropion hydrochloride formulation after being stored for at least 3, 4, 5 and/or 6 months under the same accelerated storage conditions of 40 degrees C and 75% relative humidity.

[0129] By "less degradation" it is meant any measurable decrease in the amount of at least one impurity characteristic of bupropion degradation or any measurable difference in the retention of potency relative to an otherwise similar bupropion HCl composition after being stored for at least 3, 4, 5 and/or 6 months or longer, e.g, one or two years under the afore-identified accelerated storage conditions. The "degradation products" include those listed on page 281 of the 26th edition of the USP and any other degradation products that may appear as peaks on a chromatogram during the assay that are characteristic of bupropion degradation.

[0130] As used herein "total impurities" mean all degradation products resulting from the degradation of bupropion hydrobromide. The "degradation products" include those listed on page 281 of the 26th edition of the USP and any other degradation products that may appear as peaks on a chromatogram during the assay.

[0131] 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 optional, and can be included in the dosage form to modify the properties and characteristics of the polymers used in the coat(s) or core of the dosage form for convenient processing during manufacture of the coat(s) and/or the core of the dosage form. Once the coat(s) and/or core has been manufactured, certain plasticizers can function to increase the hydrophilicity of the coat(s) and/or the core of the dosage form in the environment of use. During manufacture of the coat(s) and/or core, the plasticizer can lower the melting temperature or glass transition temperature (softening point temperature) of the polymer or binder. Plasticizers can broaden the average molecular weight of a polymer in which they are included thereby lowering 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 of the invention.

[0132] The term "moiety" as used herein is defined to mean the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), of the molecule, responsible for the physiological or pharmacological action of the drug substance.

[0133] 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".

[0134] The term "core" as used here in is defined to mean any structure that is surrounded by a wall, membrane, or coating. The wall, membrane, or coating can be a functional or non-functional coating.

[0135] 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".

[0136] The term "osmosis" as used herein refers to the flow of a solvent through a selectively-permeable membrane from a region of high solvent potential to a region of low solvent potential. The selectively-permeable membrane must be permeable to the solvent, but not to the solute, resulting in a pressure gradient across the membrane.

[0137] The term "osmotic dosage form", "osmotic delivery device", "modified release osmotic dosage form" or "controlled release osmotic dosage form" as used herein is defined to mean dosage forms which forcibly dispense the bupropion salt all or in part by pressure created by osmosis or by a combination of osmosis and diffusion of fluid into a dosage form which forces the bupropion salt to be dispensed from the osmotic dosage form. The term "osmotic dosage form", "osmotic delivery device", "modified release osmotic dosage form", or "controlled release osmotic dosage form" also encompasses such forms that can be coated with a "control releasing coat".

[0138] The terms "osmagent", "osmotic agent", "osmotically effective solute", "osmotic enhancer" "osmotically effective compounds", "osmotic solutes", or "osmotic fluid imbibing agents" are all used interchangeably herein and define any material that increases the osmotic pressure of the core, thus, increasing the hydrostatic pressure inside the osmotic dosage form. The osmagent can be either soluble or swellable and totally or partially solubilized. The osmagent can be the bupropion salt.

[0139] The term "pharmaceutically acceptable" means compatible with the treatment of subjects, in particular, humans.

[0140] The term "subject" or "patient" as used herein means all members of the animal kingdom, in particular, humans.

[0141] The term "effective amount" as used herein means a "pharmaceutically effective amount". A "pharmaceutically effective amount" is the amount or quantity of the bupropion salt or polymorph or anantiomer thereof which is sufficient to elicit an appreciable biological response when administered to a patient. It will be appreciated that the precise therapeutic dose will depend on the age and condition of the patient and the nature of the condition to be treated and will be at the ultimate discretion of the attendant physician.

[0142] As used herein, and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0143] "Palliating" a disease or disorder means that the extent and/or undesirable clinical manifestations of a disorder or a disease state are lessened and/or time course of the progression is slowed or lengthened, as compared to not treating the disorder.

[0144] The term "a" or "an" as used herein means "one" or "one or more".

The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 1 or more than 1 standard deviations, per practice in the art. Where particular values are described in the application and claims, unless otherwise stated, the term "about" means within an acceptable error range for the particular value.

[0145] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about" Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter

should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0146] Other terms are defined as they appear in the following description and should be construed in the context with which they appear.

DETAILED DESCRIPTION

[0147] There is a need for dosage forms comprising a pharmaceutically acceptable salt of bupropion that are more stable than otherwise similar compositions containing bupropion hydrochloride. Accordingly, the present invention relates to dosage forms comprising an effective amount of bupropion hydrobromide that are more stable than bupropion hydrochloride. Also, the invention encompasses polmorphs thereof and specific purified enantiomeric forms thereof. The present invention also relates to the use of such dosage forms for the treatment of one or more conditions in a subject suitable for treatment by bupropion or pharmaceutically acceptable salts thereof such as depression, obesity, smoking cessation, and other conditions treatable with bupropion such as are disclosed herein.

Formulations

[0148] The present invention encompasses any medicament containing a pharmaceutically effective amount of a stable bupropion salt according to the invention, i.e., bupropion hydrobromide. This includes both oral and non-orally administrable medicaments such as topicals, injectables, aerosols and other inhalable medicaments. Particularly such medicament compositions include orally administrable modified release dosage form containing the bupropion salt. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

[0149] "Dosage form" as used herein, means a pharmaceutical preparation that comprises an effective amount of a bupropion salt that is more stable than bupropion hydrochloride. In at least one embodiment the bupropion salt is bupropion hydrobromide.

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 losenges as well as liquid suspensions and

elixirs. Capsule dosages contain the solid composition within a capsule that can be made of gelatin or other conventional encapsulating material.

[0150] 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 design of medicaments are aware of modified release matricies conventionally used in oral pharmaceutical compositions adopted for modified release and means for their preparation. Examples of modified release formulations are disclosed in United States Patents 5,591,452 and 5,965,161.

[0151] A modified release formulation containing the bupropion salt according to the present invention can be coated with one or more functional or non-functional coatings. Examples of functional coatings include controlled release polymeric coatings (i.e. control releasing coats), moisture barrier coatings, enteric polymeric coatings, and the like. Non-functional coatings are coatings that do not affect drug release, but which affect other properties; such as the enhancement of the chemical, biological or physical stability characteristics, or the enhancement of the physical appearance of the formulation.

[0152] In at least one embodiment of the present invention the controlled release polymeric coating (or control-releasing coat) comprises 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, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

[0153] In at least one embodiment polymerizable quaternary ammonium compounds are employed in the control releasing coat, of which non-limiting examples include quaternized aminoalkyl esters and aminoalkyl amides of acrylic acid and methacrylic acid, for example β-methacryl-oxyethyl-trimethyl-ammonium methosulfate, β-acryloxy-propyl-trimethyl-ammonium chloride, and trimethylaminomethyl-methacrylamide methosulfate. The 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, styryltrialkyl ammonium salts, and the like. Other polymerizable quaternary ammonium compounds useful in the present invention include acryl- and methacryl-oxyethyltrimethyl-ammonium chloride and methosulfate, benzyldimethylammoniumethyl-methacrylate chloride, diethylmethylammoniumethyl-acrylate and -methacrylate methosulfate, N-trimethylammoniumpropylmethacrylamide chloride, and N-trimethylammonium-2,2-dimethylpropyl-1-methacrylate chloride.

[0154] In at least one embodiment the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers (such as those sold under the Trade Mark Eudragit® RS and RL) are described in National Formulary (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 hydrobromide, two or more ammonio methacrylate copolymers having differing physical properties can be incorporated. For example, it is known that by changing the molar ratio of the quaternary ammonium groups to the neutral (meth)acrylic esters, the permeability properties of the resultant coating can be modified.

[0155] In other embodiments of the present invention, the control releasing coat further includes a polymer whose permeability is pH dependent, such as anionic polymers synthesized from methacrylic acid and methacrylic acid methyl ester. Such polymers are commercially available, e.g., from Rohm Pharma GmbH under the tradename Eudragit® L and Eudragit® S. The ratio of free carboxyl groups to the esters is known to be 1:1 in Eudragit® L and 1:2 in Eudragit® S. Eudragit® L is insoluble in acids and pure water, but becomes increasingly permeable above pH 5.0. Eudragit® S is similar, except that it becomes increasingly 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 (such as Eudragit® E, commercially available from Rohm Pharma). The hydrophobic acrylic polymer coatings of the present invention can further include a neutral copolymer based on poly (meth)acrylates, such as Eudragit® NE (NE=neutral ester), commercially available from Rohm Pharma. Eudragit® NE 30D lacquer films are insoluble in water and digestive fluids, but permeable and swellable.

[0156] In at least one other embodiment of the invention, the control releasing coat comprises a dispersion of poly (ethylacrylate, methyl methacrylate) 2:1 (Kollicoat® EMM 30 D, BASF).

[0157] In at least one other embodiment of the invention, the control releasing coat comprises a polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as Kollicoat® SR30D (BASF). The dissolution profile can by 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 compounds) to the neutral (meth)acrylic esters, the permeability properties (and thus the dissolution profile) of the resultant coating can be modified.

[0158] In at least one embodiment of the invention the control releasing coat comprises ethylcellulose, which can be used as a dry polymer (such as Ethocel®, Dow Corning) solubilised in organic solvent prior to use, or as an aqueous dispersion. One suitable commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® 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 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 Aquacoat® can be intimately mixed with a suitable plasticizer prior to use. Another suitable aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). 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.

[0159] Other examples of polymers that can be used in the control-releasing coat include cellulose acetate phthalate, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium 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 of the polymer

matrix, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (molecular weight 5k to 5000k), polyvinylpyrrolidone (molecular weight 10k to 360k), anionic and cationic hydrogels, zein, polyamides, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (molecular weight 30k to 300k), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, Polyox® polyethylene oxides (molecular weight 100k to 5000k), AquaKeep® acrylate polymers, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro cellulose, carboxymethyl cellulose, cellulose ethers, methyl ethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate, gelatin, starch, maltodextrin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol 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, scleroglucan and mixtures and blends thereof.

[0160] In at least one embodiment of the invention the dosage forms are coated with polymers in order to faciliatate mucoadhsion within the gastrointestinal tract. Non-limiting examples of polymers that can be used for mucoadhesion include carboxymethylcellulose, polyacrylic acid, Carbopol ™, Polycarbophil™, gelatin and other natural or synthetic polymers.

[0161] In at least one embodiment of the invention, the dosage form is an extended release tablet comprising: (i) a core that includes bupropion hydrobromide (e.g. from 40% to 99% by weight of tablet dry weight), a binder such as polyvinyl alcohol (e.g. from 0.5% to 25% by weight of tablet dry weight), and a lubricant such as glyceryl behenate (e.g. from 0.1% to 5% by weight of tablet dry weight); and (ii) a control releasing coat that includes a water-insoluble water-permeable film-forming polymer such as ethylcellulose (e.g. from 1% to 12% by weight of tablet dry weight), a water-soluble polymer such as polyvinylpyrrolidone (Povidone® USP), (e.g. from 1.5% to 10% by weight of tablet dry weight), optionally a plasticizer such as dibutyl

sebacate, polyethylene glycol 4000 or a mixture thereof (e.g. from 0.5% to 4% by weight of tablet dry weight), and optionally a wax such as carnauba wax (e.g. from 0.01% to 0.05% by weight of tablet dry weight).

[0162] In at least one embodiment of the invention, the dosage form is a 174 mg XL tablet comprising: (i) a core that includes bupropion hydrobromide (e.g. 81% by weight of tablet dry weight), a binder such as polyvinyl alcohol (e.g. 3% by weight of tablet dry weight), and a lubricant such as glyceryl behenate (e.g. 3% by weight of tablet dry weight); and (ii) a control releasing coat that includes a water-insoluble water-permeable film-forming polymer such as ethylcellulose (e.g. 8% by weight of tablet dry weight), a water-soluble polymer such as polyvinylpyrrolidone (Povidone® USP), (e.g. 5% by weight of tablet dry weight), optionally a plasticizer such as dibutyl sebacate, polyethylene glycol 4000 or a mixture thereof (e.g. 3% by weight of tablet dry weight), and optionally a wax such as carnauba wax (e.g. 0.03% by weight of tablet dry weight).

[0163] In at least one embodiment of the invention, the dosage form is a 348 mg XL tablet comprising: (i) a core that includes bupropion hydrobromide (e.g. 87% by weight of tablet dry weight), a binder such as polyvinyl alcohol (e.g. 3% by weight of tablet dry weight), and a lubricant such as glyceryl behenate (e.g. 3% by weight of tablet dry weight); and (ii) a control releasing coat that includes a water-insoluble water-permeable film-forming polymer such as ethylcellulose (e.g. 4% by weight of tablet dry weight), a water-soluble polymer such as polyvinylpyrrolidone (Povidone® USP), (e.g. 3% by weight of tablet dry weight), optionally a plasticizer such as dibutyl sebacate, polyethylene glycol 4000 or a mixture thereof (e.g. 2% by weight of tablet dry weight), and optionally a wax such as carnauba wax (e.g. 0.01% by weight of tablet dry weight).

[0164] In addition to the modified release dosage forms described herein, other modified release technologies known to those skilled in the art can be used in order to achieve the modified release formulations of the present invention, i.e., formulations which provide a mean T_{max} of the drug and/or other pharmacokinetic parameters described herein when administered e.g., orally or by other mode of administration to human patients. Such formulations can be manufactured as a modified release oral formulation in a suitable tablet or multiparticulate formulation known to those skilled in the art. I n either case, the modified release dosage form can optionally include a

controlled release carrier which is incorporated into a matrix along with the drug, or which is applied as a controlled release coating.

Tablets

[0165] In another specific aspect of the present invention, there is provided a modified-release tablet having a core comprising a pharmaceutically acceptable salt of bupropion and conventional excipients, wherein the bupropion salt is more stable than bupropion hydrochloride (bupropion hydrobromide). The core can be surrounded by a control-releasing coat which controls the release of the bupropion salt. In other embodiments, a moisture barrier can optionally be added to surround the control-releasing coat. This moisture barrier is optional given the enhanced stability of bupropion HBr relative to bupropion HCl and by selection of an appropriate control-releasing coats and amount thereof. If present, this moisture barrier may affect in vitro drug release as well as precluding moisture from coming into contact with the buropion salt. Optionally, this tablet may further comprise one or more additional functional or non-functional coatings surrounding the core, moisture barrier and/or control-releasing coat.

Extended Release (XL) Tablets

[0166] In another specific aspect of the present invention, there is provided an extended-release (XL) tablet having a core comprising a pharmaceutically acceptable salt of bupropion and conventional excipients, wherein the bupropion salt is more stable than bupropion hydrochloride. In at least one embodiment the bupropion salt is bupropion hydrobromide. The core can be surrounded by a control-releasing coat, which controls the release of the bupropion salt. The tablet optionally may comprise one or more additional functional or non-functional coats surrounding the core or control-releasing coat. The extended-release tablet of the invention has unexpected enhanced stability.

The XL Core

[0167] The core of the extended-release tablet comprises an effective amount of a bupropion salt, a binder, and a lubricant and can contain other conventional inert excipients. In at least one embodiment the bupropion salt is bupropion hydrobromide. The amount of the bupropion salt present in the XL core can vary in an amount from 40% to 99% by weight of the tablet dry weight. For example, in certain embodiments bupropion hydrobromide is present in an amount from 70% to 95% by weight of the tablet dry weight. For example, in certain embodiments, the

core of the dosage form of the present invention comprises bupropion hydrobromide in a proportion of 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99% of the core dry weight. The tablet comprises an effective amount of bupropion salt that typically will vary from 50mg to 450 mg. For example, in certain embodiments, the tablet comprises 174mg of bupropion hydrobromide, and in other embodiments the tablet comprises 348mg of bupropion hydrobromide. In at least one embodiment of a 174mg dose tablet, the bupropion hydrobromide is present at from 75% to 85% by weight of the tablet dry weight. In at least one embodiment of a 348 mg dose tablet, the amount of bupropion hydrobromide can be present at from 80% to 90% by weight of the tablet dry weight. In certain embodiments of both the 174mg and 348mg dose bupropion hydrobromide extended-release tablets of the invention, the amount of bupropion hydrobromide is present from 90% to 99% by weight of the dry core for each dose.

[0168] A binder (also sometimes called adhesive) can be added to a drug-filler mixture to increase the mechanical strength of the 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 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 of incorporating 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 vegetable oil, castor oil, paraffin, higher aliphatic alcohols, higher alphatic 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. Specific examples of water-soluble polymer binders include modified starch, gelatin, polyvinylpyrrolidone, 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 0.5% to 25% by weight of the tablet dry weight. For example, in certain embodiments the binder is present in an amount of from 0.5% to 15% by weight of the tablet dry weight; in other embodiments from 1% to 6% by weight of the tablet dry weight; and in still other embodiments at 3% by weight of the tablet dry weight. For example, in certain embodiments of

both the 174mg and 348mg dose tablets, the binder is present in an amount of from 1% to 6% by weight of each dry core weight, and in other embodiments at 3% by weight of each dry core weight. In at least one embodiment of the invention the binder is polyvinyl alcohol.

[0169] 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 of tablets during ejection, and vertical scratches on tablet edges) and may even stop production. Accordingly, lubricants are added to certain tablet formulations of the present invention including certain embodiments of the XL tablet formulation described herein. Non-limiting examples of lubricants useful for the core include glyceryl behenate, stearic acid, hydrogenated vegetable oils (such as hydrogenated cottonseed oil (Sterotex®), hydrogenated soybean oil (Sterotex ® HM) and hydrogenated soybean oil & castor wax (Sterotex® K), stearyl alcohol, leucine, polyethylene glycol (MW 1450, suitably 4000, and higher), magnesium stearate, glyceryl monostearate, stearic acid, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax® from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, mixtures thereof and others as known in the art. In at least one embodiment of the present invention, the lubricant is glyceryl behenate (for example, Compritol® 888). The amount of lubricant present can vary from 0.1% to 6% by weight of the tablet dry weight. For example, in certain embodiments the amount of lubricant present is from 2% to 3% by weight of the tablet dry weight; and in other embodiments the amount of lubricant present is at 3% by weight of the tablet dry weight. In certain embodiments of the 174mg and 348mg dose XL tablets of the invention, the lubricant is present in an amount of 3% by weight of the tablet dry weight, or from 1% to 6% by weight of the dry core weight. For example, in certain embodiments the lubricant is present in an amount of 3% by weight of the dry core weight for both the 174mg and 348mg dose XL tablets.

[0170] At this stage, the XL core formulation of certain embodiments of the present invention, is an uncoated immediate release formulation resulting in 100% dissolution of the bupropion salt within 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 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 of the 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 of such excipients include spray dried lactose, sorbitol, mannitol, and any cellulose derivative.

[0171] In at least one embodiment of the invention, the granules to be compressed to form the core of the XL tablet of the 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 forming the granules, which are to be eventually compressed into the tablet cores, the bupropion 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 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 salt prior to the granulation step.

[0172] 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 if necessary, any other additional inert excipients, which can improve processing of the extended-release tablets of the invention. Blending of the granules with the lubricant, and if necessary, any 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 of the powder. This is especially important during tablet production at high production speeds and 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 of standard 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 as a multi-station press) fitted with suitable punches.

[0173] 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 rotary granulation.

[0174] An example of the 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 of the materials to obtain a uniform particle size for the final blend. The granulating solution is prepared by 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) of the material. A lower viscosity leads to smaller particles, and a higher viscosity leads to larger particles. In addition, the application rate (e.g. from 150 gm/min to 250 gm/min; or 200 gm/min), position of Spray gun (e.g. center position) and nozzle size (e.g. from 0.5 mm to 2mm; or 1mm) and atomization pressure (e.g. from 20 psi to 40 psi; or 30 psi) contribute further to control particle size. The active material is fluidized and heated (e.g. from 35°C to 45°C; or 40°C) prior to start of solution application. During the spray cycle, the bed temperature (e.g. from 35°C to 45°C; or 40°C) is kept at a constant temperature to avoid over-wetting. Once all the required binder solution is applied, the material is further dried to the targeted LOD value (i.e. loss on drying) (e.g. below 1%) prior to unloading. The amount of binder (e.g. polyvinyl alcohol) is between 2% to 6%, and in some cases 3%; and the solution concentration is between 3% to 7%, and in some cases 4.5 %. The time of agglomeration process for the 60 kg batch is between 45 minutes to 220 minutes, and in some cases 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 oversize particles are passed through the mill to reduce oversize particles. Oversized particles generally not to exceed 5% of total yield. The screened and milled materials are placed into a shell 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 5 min to 15 min, and in some cases 10 min). The percent lubricant is between 0.5% to 4%, and in some cases 2%. The level of lubrication is established for sufficient coverage of either larger or smaller particle size distribution. Additional characteristics include

bulk density (e.g. from 0.3 gm/ml to 0.8 gm/ml, and in some cases 0.5 gm/ml), and moisture content (e.g. not more than 1%). Particle size and flow of final blend are factors in obtaining uniform fill of cavities on a rotary press. The flow and top rotation speed of the 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 the pressure settings to obtain the required hardness. Some components monitored for the tablets are tablet thickness and friability (e.g. less than 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 specifications.

Coatings

[0175] 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 an extended release control-releasing coating ("XL Control-Releasing Coat"). In at least one other embodiment, the tablet cores are coated with an aqueous control-releasing coating that comprises an aqueous dispersion of a neutral ester copolymer without any functional groups ("AQ Control-Releasing Coat").

[0176] In certain embodiments the tablet dosage form comprises an optional moisture barrier in addition to the control-releasing coat. The control-releasing coat and the moisture barrier can be applied in two stages. The control-releasing coating can be applied directly onto the surface of the tablet cores and functions to control the release of the bupropion salt. The moisture barrier can be applied directly onto the surface of the control-releasing coat to impede or retard the absorption of moisture.

[0177] Prophetic examples of control-releasing coat formulations are provided below. It should be understood that the constituents and/or proportions of the constituents in these coatings as well as the amounts thereof may be varied in order to achieve formulations possessing 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 may be varied in order to obtain a composition possessing desired properties.

[0178] In at least one embodiment the control-releasing coat is a delayed release coating formulation for a tablet core, the coating formulation to be applied to the core comprising:

Eudragit L12.5	50% by weight of coating suspension
Triethyl citrate	0.63% by weight of coating suspension
Talc	1.25% by weight of coating suspension
Isopropyl alcohol	48.12% by weight of coating suspension

Solids total = 8.1%

Polymer content of suspension = 6.3%

[0179] Preparation of the delayed release coating formulation 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 Eudragit® L12.5 dispersion and stirred gently to avoid sedimentation. The coating is sprayed onto tablets until approximately 5mg/cm2 of Eudragit® L has been applied to the tablet core.

[0180] In at least one embodiment the control-releasing coat is a sustained release coating formulation for a tablet core, the coating formulation applied to the core comprising:

Eudragit RL 12.5	10% by weight of coating suspension
Eudragit RS 12.5	30% by weight of coating suspension
Dibutyl sebacate	0.5% by weight of coating suspension
Talc	3.5g by weight of coating suspension
Magnesium stearate	1% by weight of coating suspension
Acetone	27.5% by weight of coating suspension
Isopropyl alcohol	27.5% by weight of coating suspension

Solids total = 10%

Polymer content of suspension = 5%

[0181] Preparation of the sustained release coating formulation can be as follows: Dibutyl sebacate, talc and magnesium stearate are mixed and finely dispersed together with the diluents acetone and isopropyl alcohol. The suspension is then combined with the Eudragit® polymer dispersions. The coating is sprayed onto the core until approximately 10mg/cm2 of polymer has been applied to the core.

[0182] In at least one embodiment the control-releasing coat is a polymer blend coating possessing pH dependent polymer (Eudragit® L 30D 55) in combination with a sustained release polymer (Aquacoat®), the coating formulation applied to the core comprising:

Aquacoat (ethylcellulose 30%)	21% by weight of coating suspension
Eudragit L30 D 55	21% by weight of coating suspension
Triethyl citrate	3% by weight of coating suspension
Water	55% by weight of coating suspension

Solids total = 15.6%

Polymer content of suspension = 12.6%

[0183] Application of the polymer blend coating can be as follows: Coating applied to a 10mg/cm^2 application of polymer to the drug core.

[0184] In at least one embodiment the control-releasing coat is a drug coating (Citalopram) on top of a bupropion salt core, the coating formulation applied to the core comprising:

Kollidon VA64 (*Vinylpyrrolidone-vinyl acetate copolymer*)	2.5% by weight of drug coating suspension
Klucel ™EF (*Hydroxypropylcellulose*)	2.5% by weight of drug coating suspension
Citalopram	2% by weight of drug coating suspension
Talc	3% by weight of drug coating suspension
2-propanol	90% by weight of drug coating suspension

Solids total = 10%

Polymer content of suspension = 5%

[0185] Application of the drug coating formulation can be as follows: Drug coating is sprayed onto tablets until the desired amount of Citalopram is applied.

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 comprising:

Kollidon VA64 (*Vinylpyrrolidone-vinyl acetate copolymer*)	2.5% by weight of top-coat suspension
Klucel ™ EF	2.5% by weight of top-coat suspension

(*Hydroxypropylcellulose*)

Talc	2.5% by weight of top-coat suspension
Isopropyl alcohol	92.5% by weight of top-coat suspension

Solids total = 7.5%

Polymer content of suspension = 5%

[0186] Application of the top-coating formulation can be as follows: Coating is applied to a 2% weight gain (expressed as % of drug coated tablet core)

The Extended Relase (XL) Control-Releasing Coat

[0187] The XL control-releasing coat is a semi-permeable coat comprising a water-insoluble, water-permeable film-forming polymer, optionally a water-soluble polymer, and optionally a plasticizer.

[0188] Non-limiting examples of water-insoluble, water-permeable film-forming polymers useful for the XL control-releasing coat include cellulose ethers, cellulose esters, and polyvinyl alcohol. For example, the water-insoluble, water-permeable film forming polymers can be the ethyl celluloses, and can be selected from the following: ethyl cellulose grades PR100, PR45, PR20, PR10 and PR7 (Ethocel®, Dow), and any combination thereof. In at least one embodiment of the invention, ethyl cellulose grade PR 100 is the water-insoluble, water-permeable film-forming polymer. The amount of the water-insoluble water-permeable film-forming polymer can vary from 1% to 12% by weight of the tablet dry weight. For example, in certain embodiments the amount of the water-insoluble water-permeable film-forming polymer is present in an amount from 5% to 10%, and in other embodiments from 6% to 8% by weight of the tablet dry weight. In certain embodiments of the 174mg dose modified-release tablets of the invention, the amount of water-insoluble water permeable film-forming polymer is from 3% to 8% by weight of the tablet dry weight, and in other embodiments from 6% to 7% by weight of the tablet dry weight. With respect to the control-releasing coat itself, the amount of water-insoluble water-permeable film-forming polymer in certain embodiments of the 174mg dose tablet is from 35% to 60% by weight of the control-releasing coat dry weight, and in other embodiments from 40% to 50% by weight of the control-releasing coat dry weight. In certain embodiments of the 348mg dose modified-release tablet of the invention, the amount of water-insoluble water-permeable film-forming polymer is from 2% to 5% by weight of the tablet dry

weight, and in other embodiments from 3% to 4% by weight of the tablet dry weight. With respect to the control-releasing coat itself, the water-insoluble water-permeable film-forming polymer in certain embodiments of the 348mg dose tablet is present in an amount of 40% by weight of the control-releasing coat dry weight.

[0189] Non-limiting examples of water-soluble polymers useful for the XL control-releasing coat include polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose and mixtures thereof. In at least one embodiment the water-soluble polymer is polyvinylpyrrolidone (Povidone® USP). The amount of water-soluble polymer can vary from 1.5% to 10% by weight of the tablet dry weight. For example, in certain embodiments the amount of water-soluble polymer is from 3% to 8%, and in other embodiments at 4% by weight of the tablet dry weight. With respect to the control-releasing coat itself, in certain embodiments the amount of water-soluble polymer present is from 25% to 55% by weight of the control-releasing coat dry weight. For certain embodiments of the 174mg dose of the extended release tablet of the invention, the amount of water-soluble polymer is from 3% to 5% by weight of the tablet dry weight, and from 25% to 50% by weight of the control-releasing coat dry weight. For certain embodiments of the 348mg dose of the extended release tablet of the invention, the amount of water-soluble polymer present is from 2% to 5% of the tablet dry weight and 40% to 50% by weight of the control-releasing coat dry weight.

[0190] In certain embodiments, the XL control-releasing coat further comprises a plasticizer. The use of plasticizers 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 rssulting in various changes in polymer properties including a reduction in tensile strength, and increase in elongation and a reduction in the glass transition or softening temperature of the polymer. The amount and choice of the 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 brittleness. Once the dosage form is manufactured, certain plasticizers can function to increase the hydrophilicity of the coat(s) and/or the core of the dosage form in the environment of use (in-vitro or in-vivo). Non-limiting

examples of plasticizers that can be used in the control-releasing coat described herein 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 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 phthalate, diisononyl phthalate, 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-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, polyols (e.g. polyethylene glycol) of various molecular weights, and mixtures thereof. It is contemplated and within the scope of the invention, that a combination of plasticizers can be used in the present formulation. In at least one embodiment of the invention, the plastizer is polyethylene glycol 4000, dibutyl sebacate or a mixture thereof. The amount of plasticizer for the control-releasing coat can vary in an amount of from 0.5% to 4% by weight of the tablet dry weight. For example, in certain embodiments the plasticizer is present in an amount of from 2% to 3% by weight of the tablet dry weight. For certain embodiments of the 174 mg dose extended-release tablet of the invention, the amount of plasticizer present in the control-releasing coat is from 1% to 4% by weight of the tablet dry weight. For certain embodiments of the 348mg dose extended-release tablet of the invention, the amount of plasticizer present is from 0.5% to 4% by weight of the tablet dry weight. In certain embodiments of both the 174 mg and 348 mg dosage forms, the plasticizer is present in an amount of from 6% to 30% by weight of the control-releasing coat dry weight. For example, in certain embodiments the plasticizer is present in an amount of 12% by weight of the control-releasing coat dry weight.

[0191] The ratio of water-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer for the XL control releasing coat of the invention described herein can vary from 3:1:4 to 5:1:2. For example, in certain embodiments the ratio of water-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer for the XL control releasing coat is 4:1:3. For certain embodiments of the XL tablet the ratio of the water-insoluble water-

impermeable film-forming polymer:plasticizer:water-soluble polymer in the XL control releasing coat is from 7:2:6 to 19:5:18. In at least one embodiment the ratio of water-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer for the XL control releasing coat is 13:4:12.

[0192] Preparation and application of the XL control-releasing coat can be as follows. The water-insoluble water-permeable film-forming polymer (e.g. ethylcellulose), and the plasticizer (e.g. polyethylene glycol 4000), are dissolved in an organic solvent (e.g. a mixture of ethyl 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 control-releasing coat solution is then sprayed onto the tablet cores 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 tablet cores coated with the control-releasing coat are subsequently dried. In the manufacture of embodiments that have a moisture barrier, the control-releasing coat is dried before the moisture barrier is applied.

[0193] An example of the coating process for the XL control releasing coat is as follows: The XL control releasing 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 of the plasticizer(s) (e.g. polyethylene glycol 4000 and dibutyl sebacate). Once completely dissolved, the solution is homogenized to obtain a uniform mixture of appropriate viscosity. This procedure assures a complex mix of a water permeable film to control the release of the active drug. The composition of the solution can be formulated to contain various levels of the water insoluble polymer and water soluble polymer and a mix of the plasticizer(s). The release function is further controlled by the film thickness applied and measured as weight gain of solids in the coating required. Tablets are coated in a perforated coating pan with control of pan speed (e.g. from 8 rpm to 14 rpm, and in some cases 12 rpm), spray rate (e.g. from 150 gm/min to 250 gm/min, and in some cases 200 gm/min), atomization pressure (e.g. from 15 psi to 25 psi, and in some cases 20 psi), supply volume (from 800 to 1000 cubic ft/min, and in some cases 900 cubic ft/min), and air temperature (e.g. from 50°C to 60°C, and in some cases 55°C), monitored through a bed temperature and/or outlet temperature of from 38°C to 42°C, and in some cases 40°C. On completion of the 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 print roll or print pad onto the surface of the 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.

[0194] The skilled artisan will appreciate that controlling the permeability can control the release of the bupropion salt and/or the amount of coating applied to the tablet cores. The permeability of the XL control-releasing coat, can be altered by varying the ratio of the water-insoluble, water-permeable film-forming polymer:plasticizer:water-soluble polymer and/or the quantity of coating applied to the tablet core. A more extended release can be obtained with a higher amount of water-insoluble, water-permeable film forming polymer. The addition of other excipients to the tablet core can also alter the permeability of the control-releasing coat. For example, if it is desired that the tablet core further comprise an expanding agent, the amount of plasticizer in the control-releasing 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 of the water-insoluble water-permeable 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.

[0195] Depending on the dissolution or in-vivo release profile desired, the weight gained after coating the tablet core with the XL control-releasing coat typically will vary from 3% to 30% of the weight of the dry tablet core. For a 174 mg dose extended release tablet according to the present invention, the weight gain can typically vary from 10% to 17% of the weight of the dry tablet core. For example in certain embodiments, the weight gain is 14% of the weight of the dry tablet core. For the 348 mg dose extended release tablet of the present invention, the weight gain can vary from 7% to 10% of the weight of the dry tablet core. For example in certain embodiments, the weight gain is 9% of the weight of the dry tablet core.

AQ Control-Releasing Coat

[0196] The AQ control-releasing coat is a stable monolithic controlled release coating comprising an aqueous dispersion of a neutral ester copolymer without any functional groups, a poly glycol having a melting point greater than 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 of the poly glycol. The coating formulation is quite versatile in that it can be used to coat a variety of drug cores and can be easily manipulated to obtain the desired drug release profile.

[0197] In certain other embodiments, the AQ control-releasing coat comprises an aqueous dispersion of an ethylcellulose, a poly glycol having a melting point greater than 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 of the poly glycol. Non limiting examples of aqueous dispersions of an ethylcellulose include Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.), and Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.).

[0198] Non-limiting examples of neutral ester copolymers without any functional groups that can be used in the AQ control-releasing coat include Eudragit® NE30D, Eudragit® NE40D (Röhm America LLC), and mixtures thereof. In at least one embodiment the polymer is Eudragit NE30D, which can be present in an amount of from 1% to 35% by weight of the control-releasing coat, depending on the controlled release profile desired. Hydrophilic agents can also be included in the AQ control-releasing coat to promote wetting of the coat when in contact with gastrointestinal fluids. Non-limiting examples of such hydrophilic agents include hydrophilic water soluble polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and combinations thereof. In at 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 0.1% to 10% by weight of the coating composition. For example, in certain embodiments the hydrophilic agents are present in an amount of from 0.1% to 5%, and in other embodiments from 0.1% to 3% by weight of the control-releasing coat composition.

[0199] The AQ control-releasing coat formulation also comprises a poly gycol with a melting point of greater than 55oC. Non-limiting examples of the polyglycol include polyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 20000, and mixtures thereof. In at least one embodiment, the poly glycol is polyethylene glycol 8000. The poly glycol can be present in an amount of from 0.1% to 5% by weight of the coat. Other examples of suitable polyglycol derivatives having a melting point of at least 55°C include, but

are not limited to, Poloxamer 188, Poloxamer 338, Poloxamer 407, Polyethylene Oxides, Polyoxyethylene Alkyl Ethers, and Polyoxyethylene Stearates.

[0200] In addition to the copolymers and the poly glycol, the AQ control-releasing 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, etc. It is known in the art that depending on the intended main function, excipients can affect the properties of the coat in a series of ways, and many 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 control releasing coat composition.

[0201] The tackiness of polymeric films is a factor for the coating of solid dosage forms and for the subsequent curing step (post coating thermal treatment). During coating with either cellulosic or acrylic polymers, sometimes an unwanted, and in other times irreversible agglomeration of several granules or beads or, in the worst case, of the complete batch, can occur, especially at higher product processing temperatures. Accordingly, the addition of anti-tacking agents to coating formulations can be desirable. The anti-tacking agents which can be used include but are not limited to adipic acid, magnesium stearate, calcium stearate, zinc stearate, hydrogenated vegetable oils, sterotex, glyceryl monostearate, talc, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, and mixtures thereof. In at least one embodiment, talc is the anti-tacking agent. Talc can also function as a wetting agent. Mixtures of the anti-tacking agents are operable. The amount of anti-tacking agent in the control-releasing coat composition can be in the range from 1% to 15% by weight of the control-releasing coating dispersion. For example, in certain embodiments the anti-tacking agent is present in an amount of from 1% to 7% by weight of the control-releasing coating dispersion.

[0202] The anti-foaming agents, which can be included in the AQ control-releasing coat composition include silicon oil, simethicone, and mixtures thereof. In at least one embodiment, simethicone is the anti-foaming agent. The anti-foaming agent can be present in an amount of up to 0.5% by weight of the AQ control-releasing coat composition. For example, in certain embodiment the anti-foaming agent is present in an amount of from 0.1% to 0.4% by weight of the AQ control-releasing coat composition.

[0203] The emulsifying agent(s) (also called emulsifiers or emulgents) can be included to facilitate emulsification during manufacture of the AQ control-releasing coat, and also to 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 mono-oleate)(Tween ™ 80). The emulsifying agent(s) can be present in an amount of up to 0.5% by weight of the AQ control-releasing coat composition. For example, in certain embodiments the emulsifying agent(s) are present in an amount of from 0.1% to 0.3% by weight of the AQ control-releasing coat composition.

[0204] Colorants in the film coat formula 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 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 0.1% to 10% by weight of the AQ control-releasing coat composition. For example, in certain embodiments the pigment or colorant is present in an amount of from 0.1% to 5%, and in other embodiments from 0.1% to 2% by weight of the AQ control-releasing coat composition.

[0205] The AQ control-relasing coat can be applied onto a core comprising an effective amount of the bupropion 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 equipment suitable for film coating include: Accela Cota (Manesty Machines, Liverpool, UK), Hi-Coater (Freund Company, Japan), Driacoater (Driam Metallprodukt GmbH, Germany), HTF/150 (GS, Italy), and IDA (Dumoulin, France). Examples of units that function on a fluidized-bed principle include: Aeromatic (Fielder, Switzerland and UK) and Glatt AG (Switzerland). In at least one embodiment, the apparatus used for film coating is the Accela Cota.

[0206] The coating fluid can be delivered to the coating apparatus from a peristaltic pump at the desired rate and sprayed onto the rotating or fluidizing tablet cores. The tablet cores are pre-warmed to 30oC. During the coating process, the product temperature range is maintained

between 25oC and 35oC by adjusting the flow rate of the inlet and outlet air, temperature of the inlet air and spray rate. A single layer of coat is applied and once spraying is complete, the coated tablet cores are dried between 30oC to 40oC for 3-5 minutes at a low pan speed and low air flow. The pan is readjusted to jog speed, and drying continues for 12-15 minutes.

[0207] 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 of the melting point of the polyethylene glycol or derivative thereof. The curing temperature is preferably greater than the melting point of the polyethylene glycol or derivative thereof. The curing time is preferably 2 to 7 hours. The cured coated tablets are subsequently cooled to room temperature.

[0208] The AQ control-releasing coat is quite versatile. The length and time for the delay can be controlled by rate of hydration and the thickness of the coat. The drug release rate subsequent to the delay can be determined by the thickness and permeability of the hydrated coat. Thus, it is possible to regulate the rate of hydration and permeability of the AQ control-releasing coat so that the desired controlled-release drug profile can be achieved. 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 of the ingredients of the stable coat composition of the invention described and/or varying the curing temperature and length of curing the coated tablet cores. The skilled artisan will know which parameters or combination of parameters to change for a desired controlled release profile.

The Moisture Barrier Coat

[0209] In certain embodiments, an optional moisture barrier is applied directly onto the control-releasing coat. In other embodiments a moisture barrier coat is not included in the dosage form. The moisture barrier typically comprises an enteric polymer (e.g. acrylic polymer), a permeation enhancer and optionally a plasticizer.

[0210] In certain embodiments, the enteric polymer is an acrylic polymer. For example, the acrylic polymer can be a methacrylic acid copolymer type C [poly(methacrylic acid, methyl methacrylate) 1:1] available commercially under the trade name Eudragit® (e.g. Eudragit L 30 D-55). The methacrylic acid copolymer can be present in an amount, which can vary from 1% to 3% of the tablet dry weight and from 55% to 70% of the moisture barrier dry weight. For the 174 mg dose of the extended release tablet of the present invention, the methacrylic acid

copolymer can vary from 2% to 3% of the tablet dry weight. For example in certain embodiments, the amount of the methacrylic acid copolymer is present at 2.5% of the tablet dry weight. With respect to the moisture barrier itself, the amount of the methacrylic acid copolymer can be present in an amount of from 55% to 70% by weight of the moisture barrier dry weight. For example, in certain embodiments the methacrylic acid copolymer is present in an amount of 60% of the moisture barrier dry weight. For the 348 mg dose of the extended release tablet of the present invention, the amount of the methacrylic acid copolymer can vary from 1.5% to 3% of the tablet dry weight. For example, in certain embodiments, the amount of methacrylic acid copolymer is present at 2% by weight of the tablet dry weight. With respect to the coating itself, the methacrylic acid copolymer typically will be present in an amount of from 55% to 70% of the moisture barrier dry weight. For example, in certain embodiments the methacrylic acid copolymer is present in an amount of 60% of the moisture barrier dry weight.

[0211] 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 plasticizer. Non-limiting examples of plasticizers useful for the moisture barrier coat described herein 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 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 phthalate, diisononyl phthalate, 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-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, 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 of triethyl citrate and polyethylene glycol 4000 (e.g. Carbowax® 4000). In certain of these embodiments, the ratio of triethyl citrate to polyethylene glycol 4000

is 1:2. The plasticizer can be present in an amount which can vary from 0.2% to 0.5%. For example, in certain embodiments the plasticizer is present in an amount of from 0.2% to 0.4% of the tablet dry weight. The plasticizer can be present in an amount of 0.35% of the tablet dry weight for a 174 mg tablet; and in an amount of from 0.2% to 0.4% of the tablet dry weight for a 348 mg tablet. With respect to the moisture barrier itself, the plasticizer if present typically can be present in an amount of from 1% to 30% by weight of the moisture barrier dry weight. For example, in certain embodiments the plasticizer is present in an amount of from 10% to 14% of the moisture barrier dry weight for both the 174 mg and 348 mg dose extended release tablet of the present invention. It is well known in the art that depending on the intended main function, 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 of ways, and many substances used in tablet formulations can therefore be described as multifunctional. Thus, the polyethylene glycol used in the plasticizer combination for the moisture barrier can serve not only to increase the hydrophilicity of the moisture barrier, but can also act as a glidant.

[0212] The moisture barrier further may comprise a permeation enhancer that can increase its hydrophilicity, and can also act as a glidant. The permeation enhancer can be a hydrophilic substance and can be selected from the following: hydrophilic polymers such as hydroxypropylmethylcellulose, cellulose ethers and protein-derived materials of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. Also, synthetic water-soluble polymers can be used, such as polyvinylpyrrolidone, cross-linked polyvinyl-pyrrolidone, polyethylene oxide, etc., water-soluble polydextrose, saccharides and polysaccharides, such as pullulan, dextran, sucrose, glucose, lactose, fructose, mannitol, mannose, galactose, sorbitol and the like. In at least one embodiment of the present invention, the hydrophilic polymer comprises hydroxypropyl-methylcellulose. Other non-limiting examples of permeation enhancers include alkali metal salts such as aluminium oxidelithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, sodium citrate, and the like. The pore-forming solids can also be polymers which are soluble in the environment of use, such as Carbowaxes®, Carbopol®, and the like. The pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(a-w)alkylenediols, and the like. Other permeation enhancers which can be useful in the formulations of the 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, gum arabic, quince psyllium, flax seed, okra gum, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambda-carrageenan, gum karaya, biosynthetic gum, etc. Other pore-formers include materials useful for making microporous lamina in the 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), polychloroethers, acetal polymers, polyesters 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, poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), silicon dioxide, colloidal silica, microcrystalline cellulose and any combination thereof. In at least one embodiment of the invention the permeation enhancer is silicon doxide (e.g. Syloid® 244FP). The amount of permeation enhancer can vary from 0.5% to 1% by weight of the tablet dry weight and from 25% to 30% by weight of the moisture barrier dry weight. For the 174 mg dose extended-release tablet of the invention, the permeation enhancer can be present in an amount of 0.5% to 2% of the tablet dry weight, and from 20% to 40% by weight of the moisture barrier dry weight. For example, in certain embodiments of the 174mg dose tablet, the permeation enhancer is present in an amount of from 25% to 30% by weight of the moisture barrier dry weight. For the 348 mg dose extended release tablet of the invention, the permeation enhancer can be present in an amount which can vary from 0.5% to 2% by weight of the tablet dry weight, and from 20% to 40% by weight of the moisture barrier dry weight. For example, in certain embodiments of the 348 mg dose tablet, the permeation enhancer is present in an amount of from 25% to 30% by weight of the moisture barrier dry weight.

[0213] In at least one embodiment of the invention, the ratio of the methacrylic acid copolymer:plasticizer:permeation enhancer is 13:2:5.

[0214] The preparation and application of the moisture barrier process can be as follows. The optional plasticizer (e.g. a combination of polyethylene glycol 4000 and triethyl citrate), can be first added to water and the mixture mixed to homogeneity. The methacrylic acid co-polymer (e.g. Eudragit® L 30 D-55), 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 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 control-releasing 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.

[0215] The moisture barrier is applied to the control-releasing coated tablet cores such that the weight gain is not more than 6% of the tablet dry weight for both the 174 mg and 348 mg extended release tablets of the present invention. In at least one embodiment the weight gain is not more than 3.5% of the tablet dry weight for both 174 mg and 348 mg extended release tablets according to the present invention. The amount of the moisture barrier applied typically does not significantly render the extended release tablet described herein more resistant to gastric fluid. However, the moisture barrier can have an impact on the drug release characteristics.

[0216] The moisture barrier as used herein if present in the bupropion hydrobromide medicament typically does not function as an enteric coat. Even though the methacrylic acid copolymer, Eudragit® L 30 D-55, is referenced and is used in enteric coating formulations in the art, its functionality is formulation dependent and on the quantity of the 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 mucosa. 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 (0.1N HCl), no individual values of at least six experiments exceed 10% of the active drug dissolved and not less than 75% dissolved at 45 minutes in pH 6.8. The moisture barrier typically does not meet this requirement for the following reasons even though the bupropion salt (e.g. bupropion hydrobromide) is not negatively affected in acidic media nor is it

irritating the gastric mucosa: (1) to obtain enteric integrity with a film containing Eudragit® L 30 D-55, a weight gain of between 6% to 8% based on the dry polymer per dosage unit is recommended. The amount of Eudragit® L 30 D-55 solid applied onto the control-releasing coated tablet cores is not more than 6%, and in at least one embodiment, is not more than 3%, (2) if enteric integrity would be required, the dissolution test for the finished product (i.e., the moisture barrier coated tablet cores) at the 2 hour time point would not stipulate a limit of no more than 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.

[0217] The XL tablet of the invention provides an extended release of the bupropion salt. Generally no pore forming agent is present in the XL coating formulation. An extended release bupropion hydrobromide formulation is provided such that after 2 hours, not more than 20% of the bupropion hydrobromide content is released. For example, in certain embodiments, from 2% to 18%, from 4% to 8%, or 5% of the bupropion hydrobromide content is released after 2 hours. After 4 hours, from 15% to 45% of the bupropion hydrobromide content is released. For example, in certain embodiments from 21% to 37%, from 28% to 34%, or 32% of the bupropion hydrobromide content is released after 4 hours. After 8 hours, 40% to 90% of the bupropion hydrobromide content is released. For example, in certain embodiments from 60% to 85%, from 68% to 74%, or 74% of the bupropion hydrobromide content is released after 8 hours. After 16 hours not less than 80% of the bupropion hydrobromide content is released. For example, in certain embodiments not less than 93%, not less than 96%, or not less than 99% of the bupropion hydrobromide content is released.

[0218] Also, extended release tablets are provided wherein after 2 hours not more than 40% (e.g., 33%) of the bupropion hydromide is released; after 4 hours from 40-75% of the bupropion hydrobromide is released (e.g., 59%); after 8 hours at least 75% of the bupropion hydrobromide is released (e.g., 91%); and after 16 hours at least 85% of the bupropion hydrobromide is released (e.g., 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 are well known to those skilled in the art. Such dissolution media, dissolution conditions and aparatus for use therein are disclosed in the United States Pharmacopoeia (USP) and European and Japanese counterparts thereof. Additionally, specific examples thereof are provided in this application.

Enhanced Absorption (EA) Tablets

[0219] In another aspect of the present invention, there is provided an enhanced absorption (EA) tablet having a core comprising a pharmaceutically acceptable salt of bupropion and conventional excipients, wherein the bupropion salt is more stable than bupropion hydrochloridesuch as bupropion hydrobromide. The core is surrounded by an EA coating, which controls the release of the bupropion salt. In certain embodiments, the EA coating consists of one coat. An advantage of the EA tablet includes the lessening of the amount of drug required in the composition, which in turn can lead to a reduction of side effects. The EA tablet of the invention has unexpected enhanced stability.

The EA Core

[0220] The core of the EA tablet comprises an effective amount of a bupropion salt, a binder and a lubricant, and can contain other conventional inert excipients. The amount of the bupropion salt present in the EA core can vary from 40% to 99% by weight of the tablet dry weight. For example, in certain embodiments bupropion hydrobromide is present in an amount of from 50% to 95%, and in other embodiments in an amount of from 70% to 90% by weight of the tablet dry weight. The tablet comprises an effective amount of bupropion salt that can vary from 50mg to 450 mg. For example, the EA tablet can comprise 150mg or 300mg of bupropion hydrobromide. For a 150mg dose tablet the bupropion hydrobromide can be present in an amount of from 76% to 84% by weight of the tablet dry weight. For a 300 mg dose, the amount of bupropion hydrobromide can be present in an amount of from 80% to 83% by weight of the tablet dry weight. For both the 150mg and 300mg dose bupropion hydrobromide EA tablets of the invention, the amount of bupropion hydrobromide can be present at 94% by weight of the dry core for each dose.

[0221] A binder (also sometimes called adhesive) can be added to a drug-filler mixture to increase the mechanical strength of the 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 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, (referred to as a dry binder). Solution binders are a common way of incorporating a binder into granules. In certain embodiments, the

binder used in the EA tablets is in the form of a solution binder. Non-limiting examples of binders include hydrogenated vegetable oil, castor oil, paraffin, higher aliphatic alcohols, higher alphatic 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. Specific examples of water-soluble polymer binders include modified starch, gelatin, polyvinylpyrrolidone, 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 0.5% to 25% by weight of the tablet dry weight. For example, in certain embodiments of the invention, the amount of binder present varies from 0.5% to 15% by weight of the tablet dry weight; in other embodiments from 1% to 6% by weight of the tablet dry weight; and in still other embodiments 3% by weight of the tablet dry weight. For both the 150mg and 300mg dose EA tablets, the amount of binder can be present in an amount of from 1% to 6% by weight of each dry core weight. For example, in certain embodiments the amount of binder is present in an amount of 3% by weight of each dry core weight. In at least one embodiment of the invention the binder is polyvinyl alcohol.

[0222] 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 of tablets during ejection, and vertical scratches on tablet edges) and may even stop production. Accordingly, lubricants can be added to certain tablet formulations of the present invention including the EA tablet formulation described herein. Non-limiting examples of lubricants useful for the EA core include glyceryl behenate, stearic acid, hydrogenated vegetable oils (such as hydrogenated cottonseed oil (Sterotex®), hydrogenated soybean oil (Sterotex ® HM) and hydrogenated soybean oil & castor wax (Sterotex® K), stearyl alcohol, leucine, polyethylene glycol (MW 1450, suitably 4000, and higher), magnesium stearate, glyceryl monostearate, stearic acid, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax® from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and others as known in the art. In at least one embodiment of the invention, the lubricant is glyceryl behenate (e.g. Compritol® 888). The amount of lubricant

present can vary from 0.1% to 6% by weight of the tablet dry weight. For example, in certain embodiments the amount of lubricant present is 3% by weight of the tablet dry weight. For certain embodiments of the 174mg and 348mg dose EA tablets of the invention the lubricant is present in an amount of 3% by weight of the tablet dry weight and from 1% to 6% by weight of the dry core weight. For example, in certain embodiments the lubricant is present in an amount of 3% by weight of the dry core weight for both the 174mg and 348mg dose EA tablets.

[0223] At this stage, the EA core formulation is an uncoated immediate release formulation resulting in 100% dissolution of the bupropion salt within 1 hour. In at least one embodiment the EA core is a normal release matrix formulation. In certain embodiments the core comprises an effective amount of bupropion hydrobromide, a binder (e.g. polyvinyl alcohol), and a lubricant (e.g. glyceryl behenate). However, if necessary, additional inert excipients consistent with the objects of the invention can be added to the core formulation. The additional inert excipients can be added to facilitate the preparation and/or improve patient acceptability of the final EA bupropion salt 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 of such excipients include spray dried lactose, sorbitol, mannitol, and any cellulose derivative.

[0224] In certain embodiments, the granules to be compressed to form the core of the EA tablet of the 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 forming the granules, which are to be eventually compressed into the tablet cores, the bupropion salt is first granulated, for example with a solution binder, in a granulator, for example a fluidized bed granulator such as a fluidized bed granulator manufactured by Glatt (Germany) or Aeromatic (Switzerland). The binder (e.g. polyvinyl 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 salt prior to the granulation step.

[0225] 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 if necessary, any other additional inert excipients, which can improve processing of the EA tablets of the invention. Blending of the granules with the lubricant, and if necessary, any 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 of the powder. This is especially important during tablet production at high production speeds and 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 of standard techniques and equipment well known to the skilled artisan. In certain embodiments the tablet cores are obtained by a rotary press (also referred to as a multi-station press) fitted with suitable punches.

[0226] 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 rotary granulation.

[0227] An example of the granulation process for the EA cores (60kg batch) is as follows: A Fluid Bed Processor is used for granulation in order to agglomerate the particles of the materials to obtain a uniform particle size for the final blend. The granulating solution is prepared by 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) of the material. A lower viscosity leads to smaller particles, and a higher viscosity leads to larger particles. In addition, the application rate (e.g. from 150 gm/min to 250 gm/min; or 200 gm/min), position of Spray gun (e.g. center position) and nozzle size (e.g. from 0.5 mm to 2mm; or 1mm) and atomization pressure (e.g. from 20 psi to 40 psi; or 30 psi) contribute further to control particle size. The active material is fluidized and heated (e.g. from 35°C to 45°C; or 40°C) prior to start of solution application. During the spray cycle, the bed temperature (e.g. from 35°C to 45°C; or 40°C) is kept at a constant temperature to avoid over-wetting. Once all the required binder solution is applied, the material is further dried to the targeted LOD value (i.e. loss on drying) (e.g. below 1%) prior to unloading. The amount of binder (e.g. polyvinyl alcohol) is between 2% to 6%, and in some cases 3%; and the solution concentration is between

3% to 7%, and in some cases 4.5 %. The time of agglomeration process for the 60 kg batch is between 45 minutes to 220 minutes, and in some cases 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 oversize particles are passed through the mill to reduce oversize particles. Oversized particles generally not to exceed 5% of total yield. The screened and milled materials are placed into a shell 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 5 min to 15 min, and in some cases 10 min). The percent lubricant is between 0.5% to 4%, and in some cases 2%. The level of lubrication is established for sufficient coverage of either larger or smaller particle size distribution. Additional characteristics include bulk density (e.g. from 0.3 gm/ml to 0.8 gm/ml, and in some cases 0.5 gm/ml), and moisture content (e.g. not more than 1%). Particle size and flow of final blend are factors in obtaining uniform fill of cavities on a rotary press. The flow and top rotation speed of the 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 the pressure settings to obtain the required hardness. Some components monitored for the tablets are tablet thickness and friability (e.g. less than 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 specifications.

The EA Tablet Coating

[0228] The EA tablet cores can be coated in one stage. The EA coating is applied directly onto the surface of the tablet cores and functions to control the release of the bupropion salt.

[0229] 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.

[0230] Non-limiting examples of water-insoluble, water-permeable film-forming polymers useful for the EA coating include cellulose ethers, cellulose esters, polyvinyl alcohol and mixtures thereof. In certain embodiments, the water-insoluble, water-permeable film forming polymers are the ethyl celluloses, and can be selected from the following: ethyl cellulose grades

PR100, PR45 PR20, PR10 and PR7 (Ethocel®, Dow) and combinations thereof. In at least one embodiment ethyl cellulose grade PR 100 is the water-insoluble, water-permeable film-forming polymer. The amount of the water-insoluble water-permeable film-forming polymer can vary from 1% to 8% by weight of the tablet dry weight. For example, in certain embodiments the amount of the water-insoluble water-permeable film-forming polymer is from 2% to 6% by weight of the tablet dry weight. For certain embodiments of the 174 or 348 mg dose EA tablets of the invention, the amount of water-insoluble water permeable film-forming polymer is from 1% to 15% by weight of the tablet dry weight. For example, in certain embodiments of the 174mg dose EA tablets, the amount of the water-insoluble water-permeable film-forming polymer is present at 10.5% by weight of the tablet dry weight. With respect to the EA coat itself, the amount of water-insoluble water-permeable film-forming polymer in certain embodiments of the 174mg dose EA tablets is from 35% to 60% by weight of the EA coat dry weight. For example, in certain embodiments of the 174mg dose EA tablet, the amount of water-insoluble water-permeable polymer is present at 55% by weight of the EA coat dry weight. For certain embodiments of the 348 mg dose EA tablet of the invention, the amount of water-insoluble water-permeable film-forming polymer is from 1% to 8% by weight of the tablet dry weight. For example, in certain embodiments of the 300mg dose EA tablet, the amount of water-insoluble water-permeable film forming polymer is present at 6.3% by weight of the tablet dry weight. 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 55% by weight of the EA coat dry weight.

[0231] In certain embodiments, the EA coat further comprises a plasticizer. Non-limiting examples of plasticizers that can be used in the EA coat described herein 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 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 phthalate, diisononyl phthalate, 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-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, and mixtures thereof. polyols (e.g. polyethylene glycol) of various molecular weights, and mixtures thereof. The amount of plasticizer for the EA coat can vary in an amount from 0.5% to 4% by weight of the tablet dry weight. In a further embodiment of the invention, when a mixture of two plasticizers are used, the ratio of the two plasticizers can range from 5:95 to 95:5. In at least one embodiment of the invention, the plasticizer is polyethylene glycol 4000, dibutyl sebacate, or a mixture thereof. The ratio of polyethylene glycol 4000:dibutyl sebacate can range from 5:95 to 95:5. For certain embodiments of the 174 mg dose EA tablet of the invention, the amount of plasticizer present in the EA coat is from 0.5% to 4% by weight of the tablet dry weight. For example, in certain embodiments of the 174 mg dose EA tablet, the amount of plasticizer is present at 3.1% by weight of the tablet dry weight. For certain embodiments of the 348 mg dose EA tablet of the invention, the amount of plasticizer present is from 0.5% to 3% by weight of the tablet dry weight. For example, in certain embodiments of the 348 mg dose EA tablet, the amount of plasticizer is present at 2.0% by weight of the tablet dry weight. For certain embodiments of both the 174 mg and 348 mg dosage forms, the plasticizer is present in an amount of from 6% to 30% by weight of the EA coat dry weight. For example, in certain embodiments the amount of plasticizer is present at 17% by weight of the EA coat dry weight.

[0232] Non-limiting examples of water-soluble polymers useful for the EA coat include polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose and mixtures thereof. In at least one embodiment of the invention, the water-soluble polymer is polyvinylpyrrolidone (e.g. Povidone® USP) the amount of which can vary from 1.5% to 10% by weight of the tablet dry weight. With respect to the EA coat itself, the amount of water-soluble polymer present can vary from 20% to 50% by weight of the EA coat dry weight. For certain embodiments of the 174 mg dose of the EA tablet of the invention, the amount of water-soluble polymer present is from 1.5% to 10% by weight of the tablet dry weight or from 20% to 50% by weight of the EA coat dry weight. For example, in certain embodiments of the 174 mg dose EA tablet, the water-soluble polymer is present in an amount of 28% by weight of the EA coat dry weight. For certain embodiments of the 348 mg dose of the EA tablet of the invention, the amount of water-soluble polymer present is from 1.5% to 10% of the tablet dry weight and

from 20% to 50% by weight of the EA coat dry weight. For example, in certain embodiments of the 300 mg dose EA tablet, the water-soluble polymer is present in an amount of 28% by weight of the EA coat dry weight.

[0233] The ratio of water-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer for the EA tablet coating typically will vary from 3:1:4 to 5:1:2. For example in certain embodiments the ratio of water-insoluble water-permeable film forming polymer:plasticizer:water-soluble polymer for the EA tablet coating is 4:1:3. In at least one embodiment of the EA tablet coating, the ratio of the water-insoluble water-impermeable film-forming polymer:plasticizer:water-soluble polymer is from 7:2:6 to 19:5:18, and in other embodiments is 13:4:12.

[0234] Preparation and application of the EA coat can be as follows. The water-insoluble water-permeable film-forming polymer, (e.g. ethylcellulose), and the plasticizer (e.g. polyethylene glycol 4000, dibutyl sebacate, or a mixture thereof), are dissolved in an organic solvent (e.g. ethyl alcohol). The water-soluble polymer (e.g. polyvinyl pyrrolidone) is next added until a homogenous mixture is achieved. The resulting control-releasing coat solution is then sprayed onto the tablet cores 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 tablet cores coated with the EA coat are subsequently dried before a moisture barrier is applied.

[0235] The skilled artisan will appreciate that controlling the permeability can control the release of the bupropion salt and/or the amount of coating applied to the tablet cores. The permeability of the EA coat can be altered by varying the ratio of the water-insoluble, water-permeable film-forming polymer:plasticizer:water-soluble polymer and/or the quantity of coating applied to the tablet core. A more extended release can be obtained with a higher amount of water-insoluble, water-permeable film forming polymer. The addition of other excipients to the tablet core can also alter the permeability of the EA coat. For example, if it is desired that the tablet core further comprise an expanding agent, the amount of plasticizer in the control-releasing coat should 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 of the water-insoluble water-permeable film forming polymer and water-soluble polymer may also have to be altered depending on whether a faster or slower dissolution and/or release profile is desired.

[0236] Depending on the dissolution or in-vivo release profile desired, the weight gained after coating the tablet core with the EA coat can vary from 3% to 30% of the weight of the dry tablet core. For certain embodiments of the 174 mg dose EA tablet of the invention the weight gain is from 8% to 20% of the weight of the dry tablet core. For example, in certain embodiments of the 174 mg dose EA tablet, the weight gain is 14% of the weight of the dry tablet core. For certain embodiments of the 348 mg dose EA tablet of the invention the weight gain is from 10% to 15% of the weight of the dry tablet core. For example, in certain embodiments of the 348mg dose EA tablet, the weight gain is 13% of the weight of the dry tablet core.

[0237] The EA tablet of the invention provides an enhanced-absorption of the bupropion salt wherein typically no pore forming agent is present in the formulation. An enhanced absorption bupropion hydrobromide formulation is provided such that after 2 hours, not more than 25% of the bupropion hydrobromide content is released. For example, in certain embodiments from 10% to 20% of the bupropion hydrobromide content is released after 2 hours. After 4 hours, 25% to 55% of the bupropion hydrobromide content is released. For example, in certain embodiments from 30% to 50% of the bupropion hydrobromide content is released after 4 hours. After 8 hours, more than 60% of the bupropion hydrobromide content is released. For example, in certain embodiments from 70% to 90% of the bupropion hydrobromide content is released after 8 hours. After 16 hours more than 70% of the bupropion hydrobromide content is released. For example, in certain embodiments more than 80% of the bupropion hydrobromide content is released after 16 hours.

[0238] In addition in some embodimentsthe invention provides enhanced absorption fomulations wherein not more than 40% is released after 2 hours (e.g, 33%); after 4 hours from 40-75% is released (e.g., 59%); after 8 hours at least 75% is released (e.g., 91%); and after 16 hours at least 85% is released (e.g., 97%).

Controlled Release Matrix

[0239] In other embodiments of the 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 compositon. In this embodiment controlled release matrices contain an effective amount of a bupropion salt and at least one pharmaceutically acceptable excipient. The amount of the bupropion salt present in the

controlled release matrix can vary in an amount of from 40% to 90% by weight of the matrix tablet dry weight. For example, in certain embodiments bupropion hydrobromide is present in an amount from 60% to 80%, and in other embodiment at 70% by weight of the 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 a bupropion salt or other 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 but which affect other properties (e.g., they may enhance the chemical, biological, or the physical appearance of the controlled release formulation). Those skilled in the pharmaceutical art and the design of medicaments are well aware of controlled release matrices conventionally used in oral pharmaceutical compositions adopted for controlled release and means for their preparation. Examples of controlled release matrices are described in U.S. Patents No.'s 6,326,027; 6,340,475; 6,905,709; 6,645,527; 6,576,260; 6,326,027; 6,254,887; 6,306,438; 6,129,933; 5,891,471; 5,849,240; 5,965,163; 6,162,467; 5,567,439; 5,552,159; 5,510,114; 5,476,528; 5,453,283; 5,443,846; 5,403,593; 5,378,462; 5,350,584; 5,283,065; 5,273,758; 5,266,331; 5,202,128; 5,183,690; 5,178,868; 5,126,145; 5,073,379; 5,023,089; 5,007,790; 4,970,075; 4,959,208; 4,59,208; 4,861,598; 4,844,909; 4,834,984; 4,828,836; 4,806,337; 4,801,460; 4,764,378; 4,421,736; 4,344,431; 4,343,789; 4,346,709; 4,230,687; 4,132,753; 5,591,452; 5,965,161; 5,958,452; 6,254,887; 6,156,342; 5,395,626; 5,474,786; and 5,919,826.

[0240] Suitable excipient materials for use in such controlled release matrices 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 glyceryl monostearate, mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex, Eastman Fine Chemical Company), glycerylmonooleate, a mixture of mono, di and tri-glycerides (ATMUL 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 6to 30 carbon atoms; in certain embodiments at least 12 carbon atoms, and in other embodiments from 12 to 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 3-carbon rings or 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, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, montanic acid and melissic acid. Also useful are unsaturated monoolefinic straight chain monocarboxylic acids. Non-limiting examples of these include oleic acid, gadoleic acid and erucic acid. Also useful are unsaturated (polyolefinic) straight chain monocaboxyic acids. Non-limiting examples of these include linoleic acid, linolenic acid, arachidonic acid and behenolic acid. Useful branched acids include, for example, diacetyl tartaric acid. Non-limiting examples of long chain carboxylic acid esters include glyceryl monostearates; glyceryl monopalmitates; mixtures of glyceryl monostearate and glyceryl monopalmitate (Myvaplex 600, Eastman Fine Chemical Company); glyceryl monolinoleate; glyceryl monooleate; mixtures of glyceryl monopalmitate, glyceryl monostearate glyceryl monooleate and glyceryl monolinoleate (Myverol 18-92, Eastman Fine Chemical Company); glyceryl monolinolenate; glyceryl monogadoleate; mixtures of glyceryl monopalmitate, glyceryl monostearate, glyceryl monooleate, glyceryl monolinoleate, glyceryl monolinolenate and glyceryl monogadoleate (Myverol 18-99, Eastman Fine Chemical Company); acetylated glycerides such as distilled acetylated monoglycerides (Myvacet 5-07, 7-07 and 9-45, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company); mixtures of propylene glycol monoesters, distilled monoglycerides, sodium stearoyl lactylate and silicon dioxide (Myvatex TL, Eastman Fine Chemical Company) d-alpha tocopherol polyethylene glycol 1000 succinate (Vitamin E TPGS, Eastman Chemical Company); mixtures of mono- and diglyceride esters such as Atmul (Humko Chemical 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 of long chain carboxylic acids; polyglycerol esters of long chain carboxylic acids, propylene glycol mono- and di-esters of long chain carboxylic acids; sodium stearoyl lactylate; sorbitan monostearate; sorbitan monooleate; other sorbitan esters of long chain carboxylic acids; succinylated monoglycerides; stearyl monoglyceryl citrate; stearyl heptanoate; cetyl esters of waxes; cetearyl octanoate; C10 -C30 cholesterol/lavosterol esters; sucrose long chain carboxylic acid esters; and mixtures thereof.

[0241] The alcohols useful as excipient materials for controlled release matrices can include the hydroxyl forms of the carboxylic acids exemplified above and also cetearyl alcohol.

[0242] In addition, waxes can be useful alone or in combination with the materials listed above, as excipient materials for the controlled release matrix embodiments of the present invention. Non-limiting examples of these include white wax, paraffin, microcrystalline wax, carnauba wax, and mixtures thereof.

[0243] The lipophilic agent can be present in an amount of from 5% to 90% by weight of the controlled release matrix dosage form. For example, in certain embodiments the lipophilic agent is present in an amount of from 10% to 85%, and in other embodiments from 30% to 60% by weight of the controlled release matrix dosage form.

[0244] 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, Carbopol (B. F. Goodrich, Cleveland, Ohio), polymethacrylate polymer such as Eudragit® RL, RS, R, S, NE and E (Rhome Pharma, Darmstadt, Germany), acrylic acid polymer, methacrylic acid polymer, hydroyethyl methacrylic acid (HEMA) polymer, hydroxymethyl methacrylic acid (HMMA) polymer, polyvinyl alcohols.

[0245] The hydrophilic polymer can be present in an amount of from 10% to 90% by weight of the controlled release matrix dosage form. For example, in certain embodiments the hydrophilic polymer is present in an amount of from 20% to 75%, and in other embodiments from 30% to 60% by weight of the controlled release matrix dosage form.

[0246] In at least one embodiment, the controlled release matrix dosage form comprises hydroxypropylmethylcellulose (HPMC). HPMC is an anhydroglucose in which some of the hydroxyl groups are substituted with methyl groups to form methyl ether moieties, and others are substituted with hydroxypropyl groups or with methoxypropyl groups to form hydroxypropyl ether or methoxypropyl ether moieties. Non-limiting examples of hydroxypropyl methylcelluloses that are commercially available include METHOCEL® E (USP type 2910), METHOCEL® F (USP type 2906), METHOCEL® J (USP type 1828), METHOCEL® K (USP type 2201), and METHOCEL® 310 Series, products of The Dow Chemical Company, Midland, Mich., USA. The average degree of methoxyl substitution in these products can range from 1.3

to 1.9 (of the three positions on each unit of the cellulose polymer that are available for substitution) while the average degree of hydroxypropyl substitution per unit expressed in molar terms can range from 0.13 to 0.82. 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 of its viscosity as a 2% solution by weight in water. Different HPMC grades can be combined to achieve the desired viscosity characteristics. For example, the at least one pharmaceutically acceptable polymer can comprise two HPMC polymers such as for example Methocel® K3 LV (which has a viscosity of 3 cps) and Methocel® K100M CR (which has a viscosity of 100,000 cps). In addition, the polymer can comprise two hydroxypropylcellulose forms such as Klucel® LF and Klucel® EF. In addition, the at least one polymer can comprise a mixture of a Klucel® and a Methocel®.

[0247] 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 weights of 100,000 daltons and higher are used. Non-limiting examples of poly(ethylene oxide)s that are commercially available include: POLYOX® NF, grade WSR Coagulant, molecular weight 5 million; POLYOX® grade WSR 301, molecular weight 4 million; POLYOX® grade WSR 303, molecular weight 7 million; POLYOX® grade WSR N-60K, molecular weight 2 million; and mixtures thereof. These particular polymers are products of Dow 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.

[0248] In at least one embodiment of the controlled release matrix dosage form, PEO and HPMC are combined within the same controlled release matrix. In certain embodiments, the poly(ethylene oxide)s have molecular weights ranging from 2,000,000 to 10,000,000 Da. For example, in at least one embodiment the polyethylene oxides have molecular weights ranging from 4,000,000 to 7,000,000 Da. In certain embodiments the HPMC polymers have a viscosity within the range of 4,000 centipoise to 200,000 centipoise. For example, in at least one embodiment the HPMC polymers have a viscosity of from 50,000 centipoise to 200,000 centipoise, and in other embodiments from 80,000 centipoise to 120,000 centipoise. The relative amounts of PEO and HPMC within the controlled release matrix can vary within the scope of the

invention. In at least one embodiment the PEO:HPMC weight ratio is from 1:3 to 3:1. For example, in certain embodiments the PEO:HPMC weight ratio is from 1:2 to 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 of polymer in the matrix can constitute from 15% to 90% by weight of the matrix dosage form. For example, in certain embodiments the total amount of polymer in the matrix is from 20% to 75%, in other embodiments from 30% to 60%, and in still other embodiments from 10% to 20% by weight of the matrix dosage form.

[0249] In at least one embodiment of the invention the controlled release matrix dosage form comprises a hydrophobic polymer such as ethylcellulose. The viscosity of ethylcellulose can be selected in order to influence of rate the drug release. In certain embodiments the ethylcellulose has a viscosity from 7 to 100 cP (when measured as a 5% solution at 25oC in an Ubbelohde viscometer, using a 80:20 toluene:ethanol solvent.) In certain embodiments the hydrophobic polymer can constitute from 10% to 90% by weight of the matrix dosage form. For example, in at least one embodiment the hydrophobic polymer constitutes from 20% to 75%, and in other embodiments from 30% to 60% by weight of the matrix dosage form.

[0250] In at least one embodiment of the invention the controlled release matrix dosage form 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 alphatic 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. Non-limiting examples of water-soluble polymer binders include modified starch, gelatin, polyvinylpyrrolidone, cellulose derivatives (such as for example hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC)), polyvinyl alcohol and mixtures thereof. In at least one embodiment, the binder can be present in an amount of from 0.1% to 20% by weight of the matrix dosage form. For example, in certain embodiments the binder is present in an amount of from 0.5% to 15%, and in other embodiments from 2% to 10% by weight of the matrix dosage form.

[0251] In at least one embodiment of the invention the controlled release matrix dosage form comprises at least one lubricant. Non-limiting examples of lubricants include stearic acid,

hydrogenated vegetable oils (such as hydrogenated cottonseed oil (Sterotex®), hydrogenated soybean oil (Sterotex ® HM) and hydrogenated soybean oil & castor wax (Sterotex® K)) stearyl alcohol, leucine, polyethylene glycol (MW 1450, suitably 4000, and higher), magnesium stearate, glyceryl monostearate, stearic acid, glycerylbehenate, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax® from Union Carbide, Inc., Danbury, Conn.), 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 0 to 4% by weight of the compressed uncoated matrix. For example, in certain embodiments the lubricant is present in an amount of from 0 to 2.5 % by weight of the compressed, uncoated matrix.

[0252] In at least one embodiment of the invention the controlled release matrix dosage form comprises a plasticizer. Non-limiting examples of plasticizers 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 of from 1% to 70% by weight of the controlled release polymer in the matrix dosage form. For example, in certain embodiments the plasticizer is present in an amount of from 5% to 50%, and in other embodiments from 10% to 40% by weight of the controlled release polymer in the matrix dosage form.

[0253] In at least one embodiment of the invention the controlled release matrix dosage form comprises at least one diluent, non-limiting examples of which 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 and fatty acid salts such as magnesium stearate. In certain embodiments the diluent can be added in an amount so that the combination of the diluent and the active substance comprises up to 60%, and in other embodiments up to 50%, by weight of the composition.

[0254] In at least one embodiment of the invention the controlled release matrix dosage form comprises a solubilizer. The solubilizer can act to increase the instantaneous solubility of the bupropion salt. The solubilizer can be selected from hydrophilic surfactants or lipophilic

surfactants or mixtures thereof. The surfactants can be anionic, 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 hydrophilic transesterification products of a polyol with at least one member of the group from triglycerides, vegetable oils, and hydrogenated vegetable oils such as glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide, d-α-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 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; carnitine fatty acid ester salts; salts of alkylsulfates ; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono-and di- 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 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 of mono-and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group from 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, polyoxyethylene-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 (Capmul® by Abitec), PEG-40 hydrogenated castor oil (Cremophor RH 40® by BASF), PEG 6 corn oil (Labrafil® by Gattefosse), lauryl macrogol-32 glyceride (Gelucire44/14® by Gattefosse) stearoyl macrogol glyceride (Gelucire50/13® by Gattefosse), polyglyceryl-10 mono dioleate (Caprol® PEG860 by Abitec), propylene glycol oleate (Lutrol® by BASF), Propylene glycol dioctanoate (Captex® by Abitec), Propylene glycol caprylate/caprate (Labrafac® by Gattefosse), Glyceryl monooleate (Peceol® by Gattefrosse), Glycerol monolinoleate (Maisine® by Gattefrosse), Glycerol monostearate (Capmul® by

Abitec), PEG-20 sorbitan monolaurate (Tween20® by ICI), PEG-4 lauryl ether (Brij30® by ICI), Sucrose distearate (Sucroester7® by Gattefosse), Sucrose monopalmitate (Sucroester15® by Gattefosse), polyoxyethylene-polyoxypropylene block copolymer (Lutrol® series BASF), polyethylene glycol 660 hydroxystearate, (Solutol® by BASF), Sodium lauryl sulfate, Sodium dodecyl sulphate, Dioctyl suphosuccinate, L-hydroxypropyl cellulose, hydroxylethylcellulose, hydroxyl propylcellulose, Propylene glycol alginate, sodium taurocholate, sodium glycocholate, sodium deoxycholate, betains, polyethylene glycol (Carbowax® by DOW), d-α-tocopheryl polyethylene glycol 1000 succinate, (Vitamin E TPGS® by Eastman), and mixtures thereof. In at least one other embodiment the solubilizer can be selected from PEG-40 hydrogenated castor oil (Cremophor RH 40® by BASF), lauryl macrogol-32 glyceride (Gelucire44/14® by Gattefosse) stearoyl macrogol glyceride (Gelucire 50/13® by Gattefosse), PEG-20 sorbitan monolaurate (Tween 20® by ICI), PEG-4 lauryl ether (Brij30® by ICI), polyoxyethylene-polyoxypropylene block copolymer (Lutrol® series BASF), Sodium lauryl sulphate, Sodium dodecyl sulphate, polyethylene glycol (Carbowax® by DOW), and mixtures thereof.

[0255] In at least one embodiment of the invention the controlled release matrix dosage form comprises a swelling enhancer. Swelling enhancers are members of a special category of excipients that swell rapidly to a large extent resulting in an increase in the size of the tablet. At lower concentrations, these excipients 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 of the matrix dosage forms of the invention, examples of swelling enhancers include but are not limited to: low-substituted hydroxypropyl cellulose, microcrystalline cellulose, cross-linked sodium or calcium carboxymethyl cellulose, cellulose fiber, cross-linked polyvinyl pyrrolidone, cross-linked polyacrylic acid, cross-linked Amberlite resin, alginates, colloidal magnesium- aluminum silicate, corn starch granules, rice starch granules, potato starch granules, pregelatinised starch, sodium carboxymethyl starch and mixtures thereof. In at least one embodiment of the matrix dosage forms, the swelling enhancer is cross-linked polyvinyl pyrrolidone. The content of the swelling enhancer can be from 5% to 90% by weight of the matrix dosage form. For example, in certain embodiments the swelling enhancer is present in an amount of from 10% to 70%, and in other embodiments from 15% to 50% by weight of the matrix dosage form.

[0256] In at least one embodiment of the invention the controlled release matrix dosage form comprises additives for allowing water to penetrate into the core of the preparation (hereinafter referred to as "hydrophilic base"). In certain embodiments, the amount of water required to dissolve 1 g of the hydrophilic base is not more than 5 ml, and in other embodiments is not more than 4 ml at the temperature of 20 oC ±5oC. The higher the solubility of the hydrophilic base in water, the more effective is the base in allowing water into the core of the preparation. The hydrophilic base includes, inter 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); (e.g. PVP K30, of BASF), sugar alcohols such as D-sorbitol, 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. Cremophor RH40 produced by BASF, HCO-40 and HCO-60 produced by Nikko Chemicals Co.), polyoxyethylene-polyoxypropylene glycol (e.g. Pluronic F68 produced by Asahi Denka Kogyo K.K.), polyoxyethylene-sorbitan high molecular fatty acid ester (Tween; e.g. Tween 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, .beta.-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.

[0257] In another embodiment of the invention the controlled release matrix dosage form comprises at least one disintegrant. Non-limiting examples of disintegrants for use in the matrix dosage form include croscarmellose sodium, crospovidone, alginic acid, sodium alginate, methacrylic acid DVB, cross-linked PVP, microcrystalline cellulose, polacrilin potassium, sodium starch glycolate, starch, pregelatinized starch and the like. In at least one embodiment the disintegrant is selected from cross-linked polyvinylpyrrolidone (e.g. Kollidon® CL), cross-linked sodium carboxymethylcellulose (e.g. Ac-Di-Sol), starch or starch derivatives such as sodium starch glycolate (e.g. Explotab®), or combinations with starch (e.g. Primojel™), swellable ion-exchange resins, such as Amberlite IRP 88, formaldehyd-casein (e.g. Esma Spreng™), and mixtures thereof. In at least one embodiment the disintegrant is sodium starch glycolate. The disintegrant can be present in an amount of from 0 to 20% of the total weight of the matrix.

[0258] The controlled release matrices of the present invention can further contain one or more pharmaceutically acceptable excipients such as , granulating aids or agents, colorants, flavorants, pH adjusters, anti-adherents, glidants and like excipients conventionally used in pharmaceutical compositions.

[0259] In at least one embodiment of the invention comprising water swellable polymers formulated into the matrix, the release kinetics of the bupropion salt from the matrix are dependent upon the relative magnitude of the rate of polymer swelling at the moving rubbery/glassy front and the rate of polymer erosion at the swollen polymer/dissolution medium front. The release kinetics for the release of the bupropion salt from the matrix can be approximated by the following equation:

$M_t/M_T=kt^n$

where t is time,

M_t is the amount of the pharmaceutical agent which has been released at time t,

M_T is the total amount of the pharmaceutical agent contained in the matrix,

k is a constant, and

n is the release kinetics exponent

[0260] This equation is valid so long as n remains nearly constant. When n is equal to one, the release of the pharmaceutical agent from the matrix has zero-order kinetics. The amount of pharmaceutical agent released is then directly proportional to the time.

[0261] Where the swelling process of the 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 0.5, leading to square-root Fickian-type release kinetics.

[0262] In at least one embodiment of the invention, polymers are selected for inclusion into the formulation to achieve zero order kinetics. The release kinetics of the matrix can also be dictated by the pharmaceutical agent itself. A drug which is highly soluble can tend to be released faster than drugs which have low solubility. Where a drug has high solubility, polymer swelling and erosion must take place rapidly to maintain zero order release kinetics. If the swelling and erosion take place too slowly, the swelling process of the 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 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 large 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 of the matrix 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.

[0263] In at least one other embodiment of the invention, zero order drug release kinetics can be achieved by controlling the surface area of the 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 of the 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 of the polymer matrix composition into the aqueous medium. Thus, by adjusting the nature and amount of 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 of the coat of the unit dosage 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

(i) a matrix composition comprising (a) a polymer or a mixture of polymers, (b) a bupropion salt and, optionally, (c) one or more pharmaceutically acceptable excipients, and

(ii) a coating having at least one opening exposing at the one surface of said matrix, the coating comprising: (a) a first cellulose derivative which has thermoplastic properties and 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, and (d) a filler, the method comprising adjusting the concentration and/or the nature of the ingredients making up the matrix composition in such a manner that the diffusion rate of the aqueous medium into the matrix composition corresponds to 100%±30% such as, for example 100%±25%, 100%±20%, 100%±15% or 100%±10%, or 100% of the dissolution rate of the matrix composition so as to obtain a zero order release of at least 60% w/w such as, for example at least 65% w/w, at least 70% w/w, at least 75% w/w, at least 80% w/w, at least 85% w/w, at least 90% w/w, at least 95% w/w or at least 97% to 98% w/w of the bupropion salt from the pharmaceutical composition when subject to an in vitro dissolution test.

[0264] In at least one other embodiment of the invention, zero order drug release is approached through the use of: (a) a deposit-core comprising the bupropion salt and having defined geometric form, (b) a support-platform applied to said deposit-core, and is characterised in that said deposit-core contains, mixed with the bupropion salt, a polymeric material having a high degree of swelling on contact with water or aqueous 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 provide the mixture with suitable characteristics for its compression and for its intake of water, said support-platform comprising a polymeric material insoluble in aqueous liquids and partially coating said deposit-core.

[0265] These and further characteristics and advantages of the system according to certain embodiments of the matrix dosage form will be more apparent from the detailed description of preferred embodiments of the invention given hereinafter by way of non-limiting example. The deposit-core can generally be obtained by compressing the mixture containing the bupropion salt to a pressure of between 1000 and 4000 kg/cm^2, to thus assume a defined geometric form. Polymeric materials having a high degree of swelling can generally be cross-linked insoluble polymers, whereas gellable polymeric materials are soluble, and can control the intake of water.

[0266] 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 salt contained in the deposit-core. It is applied to a part of the external deposit-core surface chosen such as to suitably direct and quantitatively regulate the release of the bupropion salt. In this respect, as the support-

platform is impermeable to water, the polymeric material of the deposit-core in certain embodiments can swell only in that portion of the deposit not coated with the platform.

[0267] The support-platform can be obtained by compressing prechosen polymeric materials onto the deposit-core, by immersing the deposit-core in a solution of said 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, polyvinylalcohols etc. This platform can have a thickness of between 2 mm if applied by compression and 10 microns if applied by spraying or immersion, and comprises from 10% to 90% of the total surface of the system.

[0268] A factor in controlling the release of the bupropion salt is the intensity and duration of the 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, executing and regulating the release of the bupropion 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 of the 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 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 to the extent of between 5% and 80% by weight, and said gellable polymer to the extent of between 10% and 90% by weight, with respect to the mixture forming the deposit-core.

[0269] A further control factor is the geometry of the support-platform, which limits the swelling of the deposit and directs the emission of material from it. Within the scope of these embodiments it is possible to conceive many systems for the controlled release of bupropion salt, which base their operation on the swelling force and differ from each other by the type of support-platform used.

[0270] In at least one other embodiment of the invention designed to achieve zero order release of the bupropion 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 salt is first granulated with or encapsulated in 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 diffusion rate coefficient of the 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. It is this general difference in rates of diffusion between the first and second polymers which 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 of is between 2:7 and 4:5, and gelatin is present as the less swellable polymer.

[0271] In at least one other embodiment of the 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 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 of the 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 of the bupropion salt, the method comprising blending bupropion hydrobromide with 5% to 25% by weight of hydrophillic polymer, and 1% to 25% by weight of hydrophobic polymer, adding suitable pharmaceutical excipients, surface active agents and lubricants, granulating the mixture with solvents such as isopropyl alcohol, drying the granular mixture, milling the dried mixture, adding from 5% to 70% by weight of ethylcellulose, 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.

[0272] In another embodiment of the present invention, a swellable matrix dosage form is provided in which the bupropion salt is dispersed in a polymeric matrix that is water-swellable

rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases the bupropion salt primarily by diffusion. The rate of diffusion of the bupropion salt out of the 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 of the polymer. The swellable matrix is comprised of a relatively high molecular weight polymer that swells upon ingestion. In at 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 of time 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 of the bupropion salt in a gradual and prolonged manner by the process of solution diffusion, i.e., dissolution of the bupropion salt in the penetrating fluid and diffusion of the dissolved bupropion salt back out of the swellable matrix. The swellable matrix itself is solid prior to administration and, once administered, remains undissolved in (i.e., is not eroded by) the gastric fluid for a period of time sufficient to permit the majority of the bupropion salt to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of the bupropion salt from the swellable matrix is therefore controlled diffusion of the bupropion salt from the swellable matrix rather than erosion, dissolving or chemical decomposition of the swellable matrix.

[0273] As such, the swelling of the 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 of the drug to the stomach and small intestine so that the drug will have its full effect without colonic degradation, inactivation, or loss of bioavailability; (iii) retards the rate of diffusion of the drug long enough to provide multi-hour, controlled delivery of the drug into the stomach.

[0274] The bupropion salt in the swellable matrix can be present in an effective amount of from 0.1% to 99% by weight of the matrix. For example, in certain embodiments bupropion hydrobromide is present in the swellable matrix in an amount of from 0.1% to 90%, in other embodiments from 5% to 90%, in still other embodiments from 10% to 80%, and in even still other embodiments from 25% to 80% by weight of the swellable matrix.

[0275] The water-swellable polymer forming the swellable matrix in accordance with these embodiments of the present invention can be any polymer that is non-toxic, that swells in a

dimensionally unrestricted manner upon imbibition of water, and that provides for a modified release of the bupropion 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, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl 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 of the polymers listed in the preceding sentence, including block copolymers and grafted polymers. Specific examples of copolymers include PLURONIC® and TECTONIC®, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA.

[0276] The terms "cellulose" and "cellulosic", as used within this section regarding the swellable matrix embodiments of the present invention, can denote a linear polymer of anhydroglucose. Non-limiting examples of cellulosic polymers include alkyl-substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) 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 methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, and mixtures thereof. In terms of their viscosities, one class of alkyl-substituted celluloses includes those whose viscosity is within the range of 100 to 110,000 centipoise as a 2% aqueous solution at 20°C. Another class includes those whose viscosity is within the range of 1,000 to 4,000 centipoise as a 1% aqueous solution at 20°C. In certain embodiments the alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. In at least one embodiment the hydroxyethylcellulose is NATRASOL® 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

[0277] Polyalkylene oxides that can be used in certain embodiments of the 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 4,000,000 and higher. For example, in certain embodiment the poly(ethylene oxide) polymers have molecular weights within the range of 4,500,000 to 10,000,000, and in other embodiments have molecular weights within the range of 5,000,000 to 8,000,000. In certain embodiments the poly(ethylene oxide)s are those with a weight-average molecular weight within the range of 1x105 to 1x107, and in other embodiments within the range of 9x105 to 8x106. Poly(ethylene oxide)s are often characterized by their viscosity in solution. For example, in certain embodiments the poly(ethylene oxide)s have a viscosity range of 50 to 2,000,000 centipoise for a 2% aqueous solution at 20°C. In at least one embodiment the poly(ethylene oxide) is one or more of POLYOX® NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA. Mixtures thereof are operable.

[0278] Polysaccharide gums, both natural and modified (semi-synthetic) can be used in the swellable matrix embodiments of the present invention. Non-limiting examples include dextran, xanthan gum, gellan gum, welan gum, rhamsan gum, and mixtures thereof. In at least one embodiment the polysaccharide gum is xanthan gum.

[0279] Crosslinked polyacrylic acids that can be used in the swellable matrices of the 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 4,000 to 40,000 centipoise for a 1% aqueous solution at 25°C. Non-limiting examples of suitable crosslinked polyacrylic acids include CARBOPOL® NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples of suitable crosslinked polyacrylic acids include polymers known as WATER LOCK®, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

[0280] The hydrophilicity and water swellability of these polymers can cause the drug-containing swellable matrices to swell in size in the gastric cavity due to ingress of water 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 of drug from

the swellable matrix is primarily dependent upon the rate of water 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 of time, for example in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. Complete dissolution or decomposition may not occur until 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within 10 to 24 hours after the dosing period.

[0281] 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 40% of the drug within the swellable matrix one hour after ingestion (or immersion in the gastric fluid). In certain embodiments, the amount of polymer is such that at least 50% of the drug remains in the matrix one hour after ingestion; in other embodiments at least 60%, and in still other embodiments at least 80%, of the drug remains in the swellable matrix one hour after ingestion. In certain embodiments the drug will be substantially all released from the swellable matrix within ten hours; and in other embodiments within eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of the drug is released. In other embodiments the amount of polymer willl be such that after 2 hours no more than 40% is released; after 4 hours 40-75% is released; after 8 hours at least 75% is released and after 16 hours at least 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.

[0282] In other exemplary embodiments the swellable matrix after 2 hours will release no more than 40 % of the bupropion HBr, after 4 hours from 40-75%, after 8 hours at least 75% and after 16 hours at least 85%.

[0283] The water-swellable polymers of the swellable matrices can be used individually or in combination. Certain combinations will often provide a more controlled release of the drug than their components when used individually. Examples include cellulose-based polymers combined

with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

[0284] The benefits of this 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 0.01:99.99 to 80:20. For example, in certain embodiments the drug loadings (expressed in terms of the weight percent of drug relative to total of drug and polymer) are within the range of 15% to 80%; in other embodiments within the range of 30% to 80%; and in still other embodiments within the range of 30% to 70%. In at least one embodiment the drug loading is within the range of 0.01% to 80%, and in at least one other embodiment from 15% to 80%. In at least one embodiment the weight ratio of bupropion hydrobromide to polymer in the swellable matrix is from 15:85 to 80:20.

[0285] The formulations of the swellable matrices of the present invention can assume the form of 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 manner. For example, the microparticles can be placed in gelatin capsules known in the art as "hard-filled" capsules and "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 material should be highly soluble so that the particles are freed and rapidly dispersed in the stomach after the capsule is ingested.

[0286] In certain embodiments of the swellable matrices of the present invention, the formulation contains an additional amount of bupropion 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 recipient's bloodstream upon ingestion of the formulation without first undergoing the diffusion process 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 of the drug but not high enough to produce the transient overdosing that is characteristic of immediate release dosage forms that are not formulated in accordance with this invention.

[0287] In at least one embodiment of the 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, 6.6 or 6.7 mm (or more generally, 6.5 to 7 mm) in diameter and 9.5 or 10.25 mm (or more generally, 9 to 12 mm) in length. For three-pellet capsules, the pellets are again cylindrically shaped, 6.6 mm in diameter and 7 mm in length. For a size 00 gelatin capsule with two pellets, the pellets are cylindrical, 7.5 mm in diameter and 11.25 mm in length. For a size 00 gelatin capsule with three pellets, the pellets are cylindrical, 7.5 mm in diameter and 7.5 mm in length. In at least one other embodiment, the dosage form is a single, elongated tablet, with dimensions of 18 to 22 mm in length, 6.5 to 10 mm in width, and 5 to 7.5 mm in height. In at least one other embodiment, the dosage form is a single, elongated tablet, with dimensions of 18 to 22 mm in length, 6.5 to 7.8 mm in width, and 6.2 to 7.5 mm in height. In at least one embodiment the dimensions are 20 mm in length, 6.7 mm in width, and 6.4 mm in height. These are merely examples; the shapes and sizes can be varied considerably.

[0288] The particulate drug/polymer mixture or drug-impregnated swellable polymer matrix can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such 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 Elizabeth-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 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 extrudate to be cut into lengths.

[0289] In regards to the swellable matrices of the present invention, when microparticles are made by direct compression, the addition of lubricants can be helpful and sometimes important to promote powder flow and to prevent capping of the microparticle (breaking off of a portion of the particle) when the pressure is relieved. Non-limiting examples of suitable lubricants include magnesium stearate (in a concentration of from 0.25% to 3% by weight, and in certain embodiments less than 1% by weight, in the powder mix), and hydrogenated vegetable oil (in

certain embodiments hydrogenated and refined triglycerides of stearic and palmitic acids at 1% to 5% by weight, for example in at least one embodiment at 2% by weight). Additional excipients can be added to enhance powder flowability and reduce adherence.

[0290] Certain embodiments of the swellable matrices of the present invention can find utility when 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 of the stomach contents.

[0291] The controlled release matrices of the present invention can be manufactured by methods known in the art such as those described in the patents listed above (e.g. US Patent 5,965,161). An example of a method of manufacturing 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 of manufacturing controlled release matrices include wet granulation, dry granulation (e.g. slugging, roller compaction), direct compression,, melt granulation, and rotary granulation.

[0292] Additionally, controlled release particles which can be compressed or placed in capsules can be produced by combining the bupropion salt and a hydrophobic fusible component and/or a diluent, optionally with a release modifying 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 embodiment the hydrophobic fusible component has a melting point from 35°C to 140°C. Examples of release modifying agents include polyethylene glycol and particulate materials such as dicalcium phosphate and lactose.

[0293] In certain embodiments, controlled release matrices can be produced by mechanically working a mixture of bupropion 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 compressed into a matrix).

[0294] The amount of the hydrophobic fusible material used in the foregoing methods can range from 10% to 90% by weight. Mixers useful in such methods are known and include conventional high-speed mixers with stainless steel interiors. For example, a mixture can be processed until a bed temperature of 40°C or higher is realized, and the mixture achieves a cohesive granular texture comprising desired particle sizes.

[0295] As noted if the mixture contains agglomerates, they can be broken down using conventional methods to produce a mixture of powder and particles of the desired size which, can be size-separated using a sieve, screen or mesh of the 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 containing bupropion salt can be produced by melt processing as known in the art and combined into capsules or compressed into matrices.

[0296] 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 materials, colorants, and the like.

[0297] 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 coatings can include the XL control-releasing coat and the EA matrix coating described herein, which can further control the release of the bupropion salt and/or other drug.

[0298] 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 of the bupropion 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 of the present invention can also be used in the taste-masking coating.

[0299] In at least one embodiment of the matrix dosage form, the taste-masking coating comprises a polymer such as ethylcellulose, which can be used as a dry polymer (such as Ethocel®, Dow Corning) solubilised in organic solvent prior to use, or as an aqueous dispersion. One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp.,

Philadelphia, Pa., U.S.A.). Aquacoat® 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 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 Aquacoat is intimately mixed with a suitable plasticizer prior to use. Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). 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.

[0300] In other embodiments of the matrix dosage form, polymethacrylate acrylic polymers can be employed as taste masking polymers. In at least one embodiment, the taste masking coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the tradename Eudragit® or from BASF under the tradename Kollicoat®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames Eudragit® RL and Eudragit® RS, respectively. Eudragit® RL and Eudragit® RS are copolymers of acrylic and methacrylic esters 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 Eudragit® RL and 1:40 in Eudragit® RS. The mean molecular weight is 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® 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. Eudragit® RL/RS dispersions or solutions of the present invention can be mixed together in any desired ratio in order to ultimately obtain a taste masking coating having a desirable drug dissolution profile. Desirable controlled release formulations can be obtained, for example, from a retardant coating derived from 100% Eudragit® RL; 50% Eudragit® RL with 50% Eudragit® RS; and 10% Eudragit® RL with 90% Eudragit® RS.

[0301] In other embodiments of the matrix dosage form, the taste masking polymer can be an acrylic polymer which is cationic in character based on dimethylaminoethyl methacrylate and

neutral methacrylic acid esters (such as Eudragit® E, commercially available from Rohm Pharma). The hydrophobic acrylic polymer coatings of the present invention can further include a neutral copolymer based on poly (meth)acrylates, such as Eudragit® NE (NE=neutral ester), commercially available from Rohm Pharma. Eudragit® NE 30D lacquer films are insoluble in water and digestive fluids, but permeable and swellable.

[0302] In other embodiments of the matrix dosage form, the taste masking polymer is a dispersion of poly (ethylacrylate, methyl methacrylate) 2:1 (Kollicoat® EMM 30 D, BASF).

[0303] In other embodiments of the matrix dosage form, the taste masking polymer can be a polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as Kollicoat® SR30D (BASF).

[0304] Other taste masking polymers used in the matrix dosage forms include hydroxypropylcellulose (HPC); hydroxypropylmethylcellulose (HPMC); hydroxyethylcellulose; gelatin; gelatin/acacia; gelatin/acacia/vinvylmethylether maleic anhydride; gelatin/acacia/ethylenemaleic anhydride; carboxymethyl cellulose; polyvinvylalcohol; nitrocellulose; polyvinylalcohol-polyethylene glycol graft-copolymers; shellac; wax and mixtures thereof.

[0305] 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 of the matrix dosage forms 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 matrices of the invention with a taste-masking coating include those conventionally used in pharmaceutical processing, such as fluidized bed coating devices. The control-releasing coatings applied to the matrices can contain ingredients other than the cellulosic polymers. One or more colorants, flavorants, sweeteners, can also be used in the taste-masking coating.

[0306] In some embodiments of the matrix dosage forms a pore former can be included into the taste masking coat in order to influence the rate of release of bupropion hydrobromide from the matrix. In other embodiments, a pore former is not included in the taste masking coat. 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 of use, the pore-formers can for example be dissolved, and channels and pores are formed that fill with the environmental fluid.

[0307] For example, the pore-formers of certain embodiments of the matrix dosage forms can comprise one or more water-soluble hydrophilic polymers in order to modify the release characteristics of the formulation. Examples of suitable hydrophilic polymers used as pore-formers include hydroxypropylmetlhylcellulose, cellulose ethers and protein-derived materials of these polymers, the cellulose ethers, especially 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, and sorbitol. In at least one embodiment, the hydrophilic polymer comprises hydroxypropyl-methylcellulose.

[0308] Other non-limiting examples of pore-formers include alkali metal salts such as lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, and sodium citrate. The pore-forming solids can also be polymers which are soluble in the environment of use, such as Carbowaxes, and Carbopol. In addition, the pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, and poly(a-w)alkylenediols. Other pore-formers which can be useful in the formulations of the 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, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambda-carrageenan, gum karaya, biosynthetic gum, etc. Other pore-formers include materials useful for making microporous lamina in the 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), polychloroethers, acetal polymers, polyesters 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, poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), and mixtures thereof.

[0309] In general, the amount of pore-former included in the taste masking coatings of certain embodiments of the matrix dosage forms can be from 0.1% to 80%, by weight, 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 of the coated matrix. In at least one embodiment that uses water soluble pore formers such as hydroxypropylmethylcellulose, a taste masking polymer: pore former dry weight ratio of between 10:1 and 1:1 can be present. In certain embodiments the taste masking polymer: pore former dry weight ratio is from 8:1 to 1.5:1; and in other embodiments from 6:1 to 2:1. In at least one embodiment using Eudragit® NE30D as the taste masking polymer and a hydroxypropylmethylcellulose (approx 5cps viscosity (in a 2% aqueous solution)) such as Methocel® E5, Pharmacoat 606G as the water soluble pore former, a taste masking polymer: pore former dry weight ratio ratio of 2:1 is present.

[0310] 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 (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.

[0311] Flavorants that can be used in the taste-masking coating of certain embodiments of the matrix dosage forms include natural and synthetic flavoring liquids. An illustrative list of such 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 of these 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, 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); mixtures thereof and the like.

[0312] Sweeteners that can be used in the taste-masking coating of certain embodiments of the 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 salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Steva Rebaudiana (Stevioside); chloro 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-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.

[0313] The matrix taste masking coat can also include one or more pharmaceutically acceptable excipients such as lubricants, emulsifiers, anti-foaming agents, plasticisers, solvents and the like.

[0314] 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 the 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, polyoxyethylene, glyceryl monostearate, 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. Compritol™), Stear-O-Wet™, Myvatex ™TL and mixtures thereof. In at least one embodiment, the lubricant is selected from magnesium stearate and talc. Combinations of these lubricants are operable. The lubricant can each be present in an amount of from 1% to 100% by weight of the polymer dry weight in the taste masking coat. For example, in certain embodiments wherein the taste masking polymer is Eudragit® NE30D or Eudragit® NE40D (Rohm America LLC) together with a hydrophilic pore former, the lubricant is present in an amount of from 1% to 30% by weight of the polymer dry weight; in other embodiments from 2% to 20%; and in still other embodiments at 10% by weight of the matrix taste masking coat dry weight. In another embodiment where the taste masking polymer is ethylcellulose (Ethocel™ PR100, PR45, PR20, PR10 or PR7 polymer, or a mixture thereof), the lubricant can be present in an amount of from 10% to 100% by weight of the matrix taste-masking coat dry weight; in another embodiment from 20% to 80%; and in still another

embodiments at 50% by weight of the matrix taste masking coat dry weight. In other embodiments, the taste masking coat does not include a pore former.

[0315] 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 of the product. Emulsifying agents useful for the matrix taste masking coat composition 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 Span™ 80), and polysorbates (e.g. Tween™ 80). Combinations of emulsifying agents are operable. In at least one embodiment, the emulsifying agent is Tween™ 80. The emulsifying agent(s) can be present in an amount of from 0.01% to 5% by weight of the matrix taste masking polymer dry weight. For example, in certain embodiments the emulsifying agent is present in an amount of from 0.05% to 3%; in other embodiments from 0.08% to 1.5%, and in still other embodiments at 0.1% by weight of the matrix taste masking polymer dry weight.

[0316] Anti-foaming agent(s) can be included in the matrix taste masking coat to reduce frothing or foaming during manufacture of the 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 0.1% to 10% of the matrix taste masking coat weight. For example, in certain embodiments the anti-foaming agent is present in an amount of from 0.2% to 5%; in other embodiments from 0.3% to 1%, and in still other embodiments at 0.6% by weight of the matrix taste masking polymer dry weight.

[0317] Plasticizer(s) can be included in the matrix taste masking coat to provide increased flexibility and durability during manufacturing. Plasticisers that can be used in the matrix taste masking coat 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 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 phthalate, diisononyl phthalate, 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-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, and mixtures thereof. The plasticizer can be present in an amount of from 1% to 80% of the taste masking polymer dry weight. For example, in certain embodiments the plasticizer is present in an amount of from 5% to 50%, in other embodiments from 10% to 40%, and in still other embodiments at 20% of the taste masking polymer dry weight.

[0318] The taste-masking coating can be present in an amount of from 1% to 90% by weight of the matrix, depending upon the choice of polymer, the ratio of polymer:pore former, and the total surface area of the matrix formulation. Since a certain thickness of taste masking coating has to be achieved in order to achieve effective taste masking, the amount of taste masking polymer coating used during manufacture is related to the total surface area of the batch of uncoated matrices that requires a coating. For example, the taste masking polymer surface area coverage can range from 0.5 mg/cm2 to 20mg/cm2. For example, in certain embodiments the surface area coverage of the taste masking polymer is from 0.6 mg/cm2 to 10mg/cm2, and in other embodiments is from 1 mg/cm2 to 5mg/cm2. In at least one embodiment of the invention, Eudragit® E is employed as the taste masking polymer at a surface area coverage of 4mg/cm2.

[0319] In the absence of an accuracte determination of total surface area of a matrix, the amount of taste masking polymer to be applied can be expressed as a percentage of the uncoated matrix. For example, in certain embodiments the taste-masking coating is present in an amount of from 5% to 60%; in other embodiments from 10% to 40%; and in still other embodiments from 15% to 35% by weight of the matrix. In at least one embodiment the taste-masking coating is present in an amount of 30% by weight of the matrix.

[0320] 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 therof, and formulation methods may be varied therefrom in order to achieve different release characteristics:

[0321] In at least one embodiment, the controlled matrices comprise:

Bupropion HBr	30.0% by weight of the matrix
Hydroxypropylmethylcellulose E50	10.0% by weight of the matrix
Hydroxypropylmethylcellulose K15M	30.0% by weight of the matrix
Calcium phosphate dehydrate	9.5% by weight of the matrix
ATMUL™ 84S (*mono/di/tri glycerides*)	20.0% by weight of the matrix
Magnesium stearate	0.5% by weight of the matrix

[0322] 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 of the remainder of the 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 uniform size (to achieve uniform drying) and dry in an oven at 40°C for 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 5 minutes. The resultant mixture is tabletted on a suitable tablet press.

[0323] In at least one embodiment, the controlled release matrices comprise a deposit-core and support-platform. Preparation of the deposit-core can be as follows: Deposit-cores can be prepared using the following materials in the stated quantities:

Bupropion HBr	45.0g
hydroxypropylmethylcellulose (methocel K 100M-Colorcon)	35.0 g
mannitol	10.0 g
ethylcellulose (high viscosity-BDH)	3.75g
3.75 g magnesium stearate	1.0 g
5:1 ethanol-chloroform mixture	75.0 ml

[0324] The bupropion HBr is mixed intimately with the mannitol and hydroxypropylmethylcellulose 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 3000 kg/cm2 to obtain cylindrical deposit-cores with convex bases.

[0325] Application of the support-platform can be as follows: The support-platform can be applied by coating one or both the convex bases of the deposit-core with a solution of 15g low-permeability acrylic-methacrylic copolymer (Eudragit RS Rohm Pharma) in methylene chloride of a quantity to make up to 100 ml. Thereafter 0.3 ml of said 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.

[0326] In at least one embodiment, the matrix formulation is a PEO based tablet matrix formulation comprising:

Bupropion HBr	50%
PEO WSR Coagulant (*polyethylene oxide*)	15%
Methocel K100M (*hydroxypropylmethyl cellulose*)	15%
Avicel PH101 (*microcrystalline cellulose*)	19%
Magnesium Stearate	1%

[0327] Preparation of the PEO based tablet matrix formulation can be as follows: Excipients dry blended in an appropriate mixer and compressed into tablets using conventional apparatus.

Multiparticulates

Microparticles

[0328] In certain embodiments of the present invention, a multiparticulate system is provided which contains multiple microparticles each containing an effective amount of a bupropion salt and at least one pharmaceutically acceptable excipient. In at least one embodiment the bupropion salt is bupropion hydrobromide. The multiparticulates 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 of the dosage form. The multiparticulates or the multiple unit dosage forms can be

surrounded by one or more coatings. Examples of such coatings include polymeric controlled release coatings, delayed release coatings, enteric coatings, immediate release coatings, taste-masking coatings, extended release coatings, and non-functional coatings.

[0329] The bupropion salt in the microparticles can be present in an effective amount of from 0.1% to 99% by weight of the microparticles. For example, in certain embodiments bupropion hydrobromide is present in the microparticles in an amount of from 0.1% to 90%, in other embodiments from 5% to 90%, in still other embodiments from 10% to 80%, and in even still other embodiments from 25% to 80% by weight of the microparticle. In certain embodiments wherein the microparticles are manufactured using a spheronization process, the bupropion hydrobromide can be present in the microparticles in an amount of from 0.1% to 60%; in other such embodiments from 5% to 50%; and in still other such embodiments from 10% to 40% by weight of the microparticle. In at least one embodiment wherein the microparticles are manufactured using a spheronization process, the bupropion hydrobromide is present in the microparticle in an amount of 30% by weight of the microparticle.

[0330] In addition to the bupropion salt, the microparticles of the present invention also include at least one pharmaceutically acceptable excipient. Excipients can be added to facilitate in the preparation, patient acceptability and functioning of the dosage form as a drug delivery system. Excipients include spheronization aids, solubility enhancers, disintegrating agents, diluents, lubricants, binders, fillers, glidants, suspending agents, emulsifying agents, anti-foaming agents, flavouring agents, colouring agents, chemical stabilizers, pH modifiers, etc. Depending on the intended main function, 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 of ways, and many excipients used in compositions can thus be described as being multifunctional.

[0331] The microparticles of the present invention can be manufactured using standard techniques known to one of skill in the art. Useful microparticles include drug-layered microparticles and drug-containing microparticles.

Drug-Containing Microparticles

[0332] 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 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 insoluble in a molten mass is spray congealed to obtain discrete particles of the insoluble materials coated with the congealed substance. A further example is a fluidized bed based granulation/pelletization 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.

[0333] The drug-containing microparticles of the present invention can also be made by, for example, a spheronization process. One method of manufacturing the drug-containing microparticles is the applicant's proprietary CEFORM™ (Centrifugally Extruded & Formed Microspheres/Microparticles) technology, which is the simultaneous use of flash heat and centrifugal force, using proprietary designed equipment, to convert dry powder systems into microparticles of uniform size and shape. The production of microparticles containing an active drug using this CEFORM™ technology is described in United States Patent No. 5,683,720. This patent deals with the use of LIQUIFLASH® processing to spheronize compositions containing one or more active drugs to form LIQUIFLASH® microparticles.

[0334] With the CEFORM™ technology, the processing of the drug-containing microparticles of the present invention is carried out in a continuous fashion, whereby 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 on its axis and is heated by electrical power. The drug and excipient(s) pre-blend is fed into the center of the 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 of the Microparticle Chamber. The product is then 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 of such a process is that the microparticles are produced and collected from a dry feedstock without the use of any solvents.

[0335] 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 of the 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 of the drug. In this case, the drug and the excipients melt or become fluid simultaneously upon exposure to the heat. The molten mixture exits the head and forms microparticles, which cool as they fall to the bottom of the collection bin where they are collected.

[0336] 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 melting point than the drug with which they will be combined. Therefore the spheronizing process can be performed at lower temperatures, than the melting point of the drug. As a result, this can reduce the risk of polymeric interconversion, which can occur when using processing temperatures close to the melting point.

[0337] In a prophetic example of certain embodiments of the present invention, the manufacturing process for the microparticles can hypothetically be as follows: Spheronization aid is screened through a 425 micron (μm) screen. In at least one embodiment, the spheronization aid is distilled glyceryl monostearate (i.e. DMG-03VF). 50% of the spheronization aid 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 of the mixer, and then the remainder of the spheronization aid is added. The material is then blended in the mixer for a time from 1 minute to 30 minutes; preferably from 3 minutes to 10 minutes; and more preferably 6 minutes. The mixer motor speed is from 50 rpm to 2000 rpm; preferably from 200 rpm to 500 rpm; and more preferably 300 rpm. The chopper motor speed is from 50 rpm to 2000 rpm; preferably from 200 rpm to 500 rpm; and more preferably 400 rpm. The blended material is then spheronized in a CEFORM™ spheronizing head. The spheronizing head speed is from 5 Hz to 60 Hz; preferably from 10 Hz to 30 Hz; and more preferably 15 Hz. In at least one embodiment the CEFORM™ spheronizing head is a 5 inch head. The spheronizing head temperature is maintained at a

temperature from 70°C to 130°C; preferably from 90°C to 110°C; and more preferably 100°C. The microparticles obtained from the spinning process are then screened through a screen that is from 150μm to 800μm.

[0338] For microparticles manufactured using a spheronization process such as the CEFORM™ process, the microparticles include, in addition to the bupropion salt, at least one spheronization aid. Spheronization aids can assist the drug-containing mix to form robust durable spherical particles. Some examples of materials useful as spheronization aids include, but are not limited to glyceryl monostearate, glyceryl behenate, glyceryl dibehenate, glyceryl palmitostearate, hydrogenated oils such as hydrogenated castor oil marketed under the name Cutina ™ HR, fatty acid salts such as magnesium or calcium stearate, polyols such as mannitol, sorbitol, xylitol, stearic acid, palmitic 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 thermo-softening polymers can also function as spheronization aids. Some non-limiting examples of such thermo-plastic or thermo-softening polymers include Povidone, cellulose ethers and polyvinylalcohols. Combinations of spheronization aids can be used. In at least one embodiment, the spheronization aid is glyceryl monostearate (i.e. DMG-03VF). The spheronization aid can be present in an amount of from 0.1% to 99% by weight of the microparticle. For example, in certain embodiments the spheronization aid is present in an amount of 5% to 90%; in other embodiments from 10% to 80%; in still other embodiments from 20% to 70%; and in even still other embodiments from 30% to 60% by weight of the microparticle. In at least one embodiment the spheronization aid is present in an amount of 50% by weight of the microparticle. In at least one other embodiment, the microparticles include 50% (w/w) of bupropion hydrobromide and 50% (w/w) of the spheronization aid.

[0339] In certain embodiments, each microparticle can also include at least one solubility enhancer. Solubility enhancers can be surfactants. Certain embodiments of the invention include a solubility enhancer that is a hydrophilic surfactant. Hydrophilic surfactants can be used to provide any of several advantageous characteristics to the compositions, including: increased solubility of the buproprion salt in the microparticle; improved dissolution of the buproprion salt; improved solubilization of the bupropion salt upon dissolution; enhanced absorption and/or bioavailability of the bupropion salt. The hydrophilic surfactant can be a

single hydrophilic surfactant or a mixture of hydrophilic surfactants, and can be ionic or non-ionic.

[0340] Likewise, various other embodiments of the 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 of the advantageous characteristics listed above for hydrophilic surfactants, as well as further enhancing the function of the surfactants. These various embodiments are described in more detail below.

[0341] 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. An empirical parameter commonly used to characterize the relative hydrophilicity and lipophilicity of non-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 HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

[0342] Using HLB values as a rough guide, hydrophilic surfactants can generally be considered to be those compounds having an HLB value greater than 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic surfactants can be compounds having an HLB value less than 10.

[0343] It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as 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 (poloxamers, available commercially as PLURONIC® surfactants, BASF Corp.), the HLB values may not accurately reflect the true physical chemical nature of the compounds. Finally, commercial surfactant products 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 of the commercial product of which the compound is a major component. Different commercial products having the same primary surfactant component can, and typically do, have different

HLB values. In addition, a certain amount of lot-to-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.

[0344] Solubility enhancers can be any surfactant suitable for use in pharmaceutical compositions. Suitable surfactants can be anionic, cationic, zwitterionic or non-ionic. Such surfactants can be grouped into the following general chemical classes detailed in Tables 81-98 herein. The HLB values given in Tables 81-98 below generally represent the HLB value as reported by the manufacturer of the corresponding commercial product. In cases where more than one commercial product is listed, the HLB value in the Tables is the value as reported for one of the commercial products, a rough average of the reported values, or a value that, in the judgment of the present inventors, is more reliable.

[0345] It should be emphasized that the invention is not limited to the surfactants in Tables 81-98, which show representative, but not exclusive, lists of available surfactants. In addition, refined, distilled or fractionated surfactants, purified fractions thereof, or re-esterified fractions, are also within the scope of the invention, although not specifically listed in the Tables.

[0346] Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown in Table 81.

[0347] Polyethylene glycol (PEG) fatty acid diesters are also suitable for use as surfactants in the compositions of the present invention. Representative PEG-fatty acid diesters are shown in Table 82.

[0348] In general, mixtures of surfactants are also useful in the present invention, including mixtures of two or more commercial surfactant products. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters. Representative surfactant mixtures are shown in Table 83.

[0349] Suitable PEG glycerol fatty acid esters are shown in Table 84.

[0350] A large number of 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. In certain embodiments, the oils used are castor oil or hydrogenated castor oil or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond

oil. Examples of alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, and pentaerythritol. Representative surfactants of this class suitable for use in the present invention are shown in Table 85.

[0351] Polyglycerol esters of fatty acids are also suitable surfactants for the present invention. Examples of suitable polyglyceryl esters are shown in Table 86.

[0352] Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. Examples of surfactants of this class are given in Table 87.

[0353] In general, mixtures of surfactants are also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters are suitable and are commercially available. Examples of these surfactants are shown in Table 88.

[0354] Another class of surfactants is the class of mono- and diglycerides. These surfactants are generally lipophilic. Examples of these surfactants are given in Table 89.

[0355] Sterols and derivatives of sterols are suitable surfactants for use in the present invention. These surfactants can be hydrophilic or lipophilic. Examples of surfactants of this class are shown in Table 90.

[0356] A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in the present invention. In general, these surfactants are hydrophilic, although several lipophilic surfactants of this class can be used. Examples of these surfactants are shown in Table 91.

[0357] Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in the present invention. Examples of these surfactants are shown in Table 92.

[0358] Esters of sugars are suitable surfactants for use in the present invention. Examples of such surfactants are shown in Table 93.

[0359] Several hydrophilic PEG-alkyl phenol surfactants are available, and are suitable for use in the present invention. Examples of these surfactants are shown in Table 94.

[0360] The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and lipophilic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in the present invention. These surfactants are available under various trade names, including Synperonic™ PE series (ICI); Pluronic® series (BASF), Emkalyx™, Lutrol™ (BASF), Supronic™

Monolan™, Pluracare™, and Plurodac™. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively. Examples of suitable surfactants of this class are shown in Table 95.

[0361] Sorbitan esters of fatty acids are suitable surfactants for use in the present invention. Examples of these surfactants are shown in Table 96.

[0362] Esters of lower alcohols (C2 to C4) and fatty acids (C8 to C18) are suitable surfactants for use in the present invention. Examples of these surfactants are shown in Table 97.

[0363] Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in the present invention. In certain embodiments, the surfactant is an anionic surfactant such as a fatty acid salt, a bile salt, or a combination thereof. In other embodiments the surfactant is a cationic surfactant such as a carnitine. Examples of ionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate; lauroyl carnitine; palmitoyl carnitine; and myristoyl carnitine. Examples of such surfactants are shown in Table 98.

[0364] Ionizable surfactants, when present in their unionized (neutral, non-salt) form, are lipophilic surfactants suitable for use in the compositions of the present invention. Particular examples of such 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 of the fatty acid salts and bile salts shown in Table 98.

[0365] Derivatives of oil-soluble vitamins, such as vitamins A, D, E, K, etc., are also useful surfactants for the compositions of the present invention. An example of such a derivative is tocopheryl PEG-1000 succinate (TPGS, available from Eastman).

[0366] In certain embodiments, surfactants or mixtures of surfactants that solidify at ambient room temperature are used. In other embodiments, surfactants or mixtures of surfactants 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.

[0367] Examples of non-ionic hydrophilic surfactants include alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene

alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols with fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; polyethoxylated fat-soluble vitamins or derivatives; and mixtures thereof.

[0368] In certain embodiments, the non-ionic hydrophilic surfactant is selected from the group consisting of 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; and polyoxyethylene hydrogenated vegetable oils. The glyceride can be a monoglyceride, diglyceride, triglyceride, or a mixture thereof.

[0369] In certain other embodiments, the surfactants used are non-ionic hydrophilic surfactants that are reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils or sterols. These reaction mixtures are largely composed of the transesterification products of the 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.

[0370] The hydrophilic surfactant can also be, or include as a component, an ionic surfactant. Examples of ionic surfactants include alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fusidic acid and derivatives thereof; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate; carnitines; and mixtures thereof.

[0371] 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 of fatty acids; sodium docusate; acyl lactylates; mono-

,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-diglycerides; carnitines; and mixtures thereof.

[0372] Examples of ionic surfactants include lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate, taurochenodeoxycholate, ursodeoxycholate, tauroursodeoxycholate, glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

[0373] In certain embodiments, ionic surfactants used include lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof. In at least one embodiment, the ionic surfactant is selected from lecithin, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof.

[0374] Examples of lipophilic 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; 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; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; and mixtures thereof.

[0375] As with the hydrophilic surfactants, lipophilic surfactants can be reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

[0376] In certain embodiments, the lipophilic surfactants include one or more selected from the group consisting of 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; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; and reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, sterols, and mixtures thereof.

[0377] In certain other embodiments, the lipophilic surfactants include one or more selected from the group consisting of 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 fatty acid moiety is a C6 to C22 fatty acid.

[0378] Other embodiments include lipophilic surfactants which are the reaction mixture of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols. Examples of polyols are polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, and mixtures thereof.

[0379] Combinations of solubility enhancers (i.e. surfactants) can be used. Examples of macrogol fatty acid esters useful as solubility enhancers include Gelucire 50/13® and Gelucire 44/14®. In at least one embodiment the solubility enhancer is Gelucire 50/13®. The solubility enhancer can be present in an amount of from 0.1% to 70% by weight of the microparticle. For example, in certain embodiments, the solubility enhancer is present in an amount of from 1% to 50%; in other embodiments from 10% to 30%; in still other embodiments from 15% to 25% by

weight of the microparticle. In at least one embodiment the solubility enhancer is present in an amount of 20% by weight of the microparticle.

[0380] It is contemplated that in some embodiments, one or more other pharmaceutically acceptable excipients consistent with the objects of the present invention can be used in the microparticles, such as a lubricant, a binder, a pH modifier, a filler and/or a glidant.

[0381] The process for manufacturing the drug-containing microparticles of the present invention by spheronization are not limited to the CEFORM™ technology, and any other technology resulting in the formation of the microparticles consistent with the objects of the present invention can also be used. For example, microparticles of the invention can also be manufactured by by extrusion/spheronization, granulation or pelletization.

[0382] 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:

(i) Dry-mixing of ingredients to achieve a homogenous powder dispersion;

(ii) Wet massing using for example a high-shear wet granulator to form rod shaped particles of uniform diameter;

(iii)Extrusion to form rod-shaped particles of uniform diameter;

(iv)Spheronization to round off the rods into spherical particles;

(v) Screening to achieve the desired narrow particle size distribution.

[0383] The mixing vessel used for dry-mixing can be of any size and shape compatible with the size of the formulation to be produced. For example, commercially available mixing devices such as planetary mixers, high shear mixers, or twin cone blenders can be used. If relatively small quantities of formulation are to be prepared, a simple mortar and pestle can be sufficient to mix the ingredients. The type of mixing vessel would be apparent to one skilled in the pharmaceutical art. The moistened mass formed by wet-massing in conventional granulation equipment is extruded through a perforated mesh in order to produce cylindrical filaments. The port of the meshes can determine the diameter of the filaments. A port ranging from 0.2 mm to 3 mm can be used in this process. In at least one embodiment utilizing this process, the port ranges from 0.4 mm to 2 mm. The extrusion can be 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

extrusion/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 in spherical or quasi-spherical particles on the upper surface of the rotating plate at a velocity ranging from 200 rpm to 2,000 rpm. 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 formulations.

[0384] A prophetic example of an extrusion/spheronization formulation comprising bupropion hydrobromide can be as follows: In this example, the bupropion hydrobromide can be present in an amount of from 1% to 80% w/w. In certain embodiments within this example, the bupropion hydrobromide is present in an amount of from 1% to 50% w/w; in other embodiments from 10% to 30%; and in still other embodiments 10% w/w. In this example, the filler can be present in an amount of from 0% to 80% w/w. In certain embodiments of this example, the filler is present in an amount of from 10% to 60%; and in other embodiments at 40% w/w. In this example, the microcrystalline cellulose can be present in an amount of from 10% to 90% w/w. In certain embodiments of this example, the microcrystalline cellulose is present in an amount of from 10% to 70%; and in other embodiments from 20% to 50% w/w. In this example, the binder can be present in an amount of from 0% to 10% w/w. In certain embodiments of this example, the binder is present in an amount of from 1% to 8%; and in other embodiments from 2% to 4% w/w. In this example, water can be present in an amount of from 10% to 80% w/w. In certain embodiments of this example, water is present in an amount of from 15% to 70%; and in other embodiments from 20% to 50% w/w. Suitable fillers in this example 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. Suitable lubricants 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, sodium chloride, sodium lauryl sulfate, magnesium lauryl sulfate, sodium stearyl fumarate, glyceryl behenate and polyethylene glycol (such as Carbowax™ 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-vinylacetate copolymer (e.g. Kollidon VA64) hydroxyethylcellulose, low molecular weight hydroxypropylmethylcellulose (e.g. viscosity of 1-50 cps at 20oC; 2-12 cps at 20oC; or 4-6 cps at 20oC), hydroxypropylcellulose polymethacrylates, and mixtures thereof.

[0385] The drug-containing microparticles formed by extrusion/spheronization in this prophetic example can be produced using cross-linked amphiphilic 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 form of dry powder to which a suitable amount of liquid is added to obtain a pasty consistency; (b) 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 of the filaments in order to obtain a product in the form of spherical multiparticulates; (d) the drying of the product; and (e) the optional depositing of a drug on the surface of the microparticles. "Cross-linked amphiphilic polymer" refers in this example to polymers showing characteristics of swellability 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 of the macromolecular meshes, or chemically, thus showing points of link among the macromolecular chains. Non-limiting examples of such polymers include cross-linked polyvinyl pyrrolidone, sodium carboxymethylcellulose, sodium glycolate starch and dextrans. Optional excipients include dispersing, emulsifying, wetting agents and colouring agents. The expression "uniform mixture" in this example means that the components of the mixture are uniformly dispersed in the formulation by a mixing process which assures the uniform distribution of each component. A reasonable mixing time can range from 1 to 60 minutes using one of the mixing equipments conventionally used for the dry mixing of the powders (e.g. "V", fixed body, rotating body, sigma mixers). The term "liquid" in this example means any liquid substance or mix (solution or emulsion) of liquids of normal pharmaceutical use able to moisten the powder mix, as for example water, aqueous solutions having different pH, organic solvents of normal pharmaceutical use (e.g. alcohols, chlorinated solvents), and oils. Among the oils and surfactants 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 synthetic mono-, di- and triglycerides containing saturated and/or unsaturated

fatty acids and their polyhydroxyethylated derivatives (caprico-caprilic triglycerides [Mygliol™, Captex™, Labrafac™, Lipo], saturated or unsaturated polyhydroxylated triglycerides of various kind [Labrafil™, Labrafac™ Hydro, Gelucire™]); liquid waxes (isopropyl myristate, isopropyl-caprinate, -caprylate, -laurate, -palmitate, -stearate); 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 Labrasol™); polyglycols (propylene glycol, tetraglycol, and ethoxydiglycol (Transcutol™), sorbitan-esters of fatty acids (for example Span®, Arlacel®, Brij®), polyoxyethylenesorbitan esters of fatty acids (for example Tween®, Capmul®, Liposorb®), polypropylene oxide-polyethylene oxide (Poloxamer) copolymers, polyethylene glycol esters (PEG)-glycerol (Labrasol®, Labrafil®), PEG esters and long chain aliphatic acids or alcohols (for example Cremophor®), polyglycerid esters (Plurol®), saccharide and fatty acid esters (sucro-esters). Moreover, anionic surfactants (for example sodium lauryl sulfate, sodium stearate, sodium oleate) or cationic surfactants (for example tricetol), 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.

[0386] In a particular embodiment formed by an extrusion/spheronization process from the prophetic example described above, the moistening liquid comprises an oil/surfactant 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 of the mixture can range from 1% to 80% by weight. As a prophetic example of this embodiment, a mixture of bupropion hydrobromide and Kollidon™ CL in a ratio equal to 1/3 by weight is co-milled obtaining the mixture in the form of powder having the 100% of granulometry lower than 50 microns. The mixture is moistened using a liquid demineralized water containing Kollidon™ 25 (polyvinyl pyrrolidone, BASF) in a solution 3% w/w. The extrusion is carried out forcing the moistened mass through a threader having diameter of the holes equal to 1 mm. The operative parameters in this prophetic example can be as follows: powder flow rate: 4.5 kg/h; liquid flow rate: 4.1 kg/h; torsional stress: 27%; head temperature: 46°C; and screw rotation velocity: 140 rpm. The extrusion filaments are then processed in a spheronizator adjusted at a velocity equal to 1,000 rpm for 2 minutes. The obtained microparticles are then dried in a fluid bed for 2 hours to a maximum temperature equal to 59°C. At the end of the drying the product is discharged and is mechanically screened separating the fraction ranging from 0.7 mm to 1.2 mm.

[0387] Another prophetic example of a drug-containing microparticle embodiment of the invention formed by an extrusion/spheronization process, uses a charged resin, the steps of which can comprise: (a) adding the charged resin, bupropion hydrobromide and other excipients, to a 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 of the dry powder mixture into a wet granulation that supports subsequent extrusion and spheronization (marumerization) are included. Typically, water or aqueous solutions are employed. Alcohols, typically ethanol or isopropanol, can be included with the granulating water to enhance the workability of the granulation. In another embodiment of this invention, one or more of the components of the 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 granulating solvent to assure more uniform distribution throughout the formulation. (d) granulating the mixture until a uniform granulation results; (e) extruding the wet granulation through a screen to produce strands of granulation; (f) spheronizing the strands of granulation to produce spherical multiparticulates; and (g) collecting and drying the spherical multiparticulates. By "charged resin" is meant in this example to mean a polymer with ionizable functional groups that becomes useful in the embodiment of this invention. This broadly encompasses any polymer that upon ionization, is capable of producing cationic or anionic polymeric chains and which support spheronization. Typically from 10% to 70% by weight of the spherical multiparticulate is charged resin. Non limiting examples of these charged resins include sodium polystyrene sulfonate which is sold under the trade name AMBERLITE IRP-69™ by Rohm and Haas, Co., Philadelphia, Pa.; the chloride salt of cholestyramine resin USP, sold as AMBERLITE IRP-276™ by Rohm and Haas, Co., Philadelphia, Pa.; the acid form of methacrylic acid-divinyl benzene, sold as AMBERLITE IRP-64™ by Rohm and Haas Co., Philadelphia, Pa.; carboxypolymethylenes sold under the trade names CARBOPOL™ 974P and CARBOPOL™ 934P by B. F. Goodrich, Inc., Brecksville, Ohio, and sodium polyacrylate, sold under the trade name AQUAKEEP™ J-550 by Seitetsu Kagaku, Japan. In order for the resin to maintain the desired degree of ionization, agents which produce an acidic or basic environment during granulation and 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 tromethamine. Certain compounds can be added to the granulation to provide the proper degree of hydration of the charged resin, medicament and excipients. These hydrating agents include sugars such as lactose, sucrose, mannitol, sorbitol, pentaerythritol, glucose and dextrose. Polymers such as polyethylene glycol as well as surfactants and other organic and inorganic salts can also be used to modulate polymer hydration.

[0388] In another prophetic example, multiparticulates containing bupropion hydrobromide can be obtained as follows:

Component	**Percent w/w**
Bupropion HBr	8.7
Disodium Phosphate	7.0
Monosodium phosphate	1.7
Sodium dodecyl sulfate	21.7
Sodium Chloride	17.4
Povidone 29-32K	8.7
AMBERLITE IRP-69	34.8
Butylated Hydroxyanisol	0.0002

[0389] In this prophetic example, approximately 5.75 kg of the above formulation is mixed in a planetary mixer for 15 minutes. The butylated hydroxyanisol is dissolved in 60 cc of ethanol and water is added to bring the final solution to a volume of 133 cc. This solution is added to the planetary mixer over a two (2) minute period. The mixer is then granulated with seven aliquots of 250 cc of water added over a fifteen minute period. The granulation thus formed is extruded through a 1.0 mm screen and aliquots spheronized by marumerization at approximately 1200 rpm for approximately 10 minutes each. The spherical multiparticulates formed are then dried at 50°C for 24 hours.

[0390] Another embodiment of this 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 fall in a tower countercurrentwise to a gas; and the solid pearls are collected in the bottom of the tower. In this example, the quantity of bupropion hydrobroimde can vary from 5% to 95% by weight; and in certain embodiments from 40% to 60% by weight. The additives which enable the crystallization of the supercooled product to be 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, the glycerol stearate marketed under the mark Precirol™, the glycerol behenate marketed under the mark Compritol™, hydrogenated oils such as: hydrogenated castor oil marketed under the mark Cutina™ HR, fatty acid salts such as: magnesium or calcium stearate, polyols such as: mannitol, sorbitol, xylitol, waxes such as: white wax, carnauba wax, paraffin wax, polyoxyethylene 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 adjustable dissolution of the pearls when they are used, examples of which include: cellulose derivatives (hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, ethyl cellulose, carboxymethyl cellulose), acrylic resins (marketed under the mark Eudragit®), polyvinyl acetates (marketed under the mark Rhodopas®), polyalkylene (ethylene propylene), polylactic, maleic anhydride and silicone resins. In addition, inorganic additives can be added to accelerate the solidification of the active substances, examples of which 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 of the active substance in the crystallization additive, examples of which include: sorbitol esters, the polyoxyethylene polysorbates marketed under the mark Tween®, and glycols such as glycerine or propylene glycol. The process for the preparation of pearls comprise preparing a melt of the 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 of the constituents, possible insoluble compounds being added at the end of the melting so as to obtain a homogeneous mass. The nature of the constituents of the melt is chosen by the person skilled in the art, which is considered as a function of the compatibility of the constituents, the viscosity of the mixture of constituents, the nozzle diameter, the hydrophilicity of the active substance, the surface tension

of the active substance, the particle size of the insoluble additives, the flow rate of the nozzle, the temperature of the tower, its height and, above all, the size of the desired pearls, the proportion of bupropion hydrobromide to be included therein and the desired release time of the active substance.

[0391] Alternative procedures other than extrusion or spheronization for manufacturing drug-containing microparticles can include wet granulation, solvent granulation and melt granulation. All of these 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 excipients into granules. After granulation, the liquid can be removed by a separate drying step. Melt 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 excipients into granules. The binder thereby, can be incorporated into the granules when the granules cool.

[0392] Certain embodiments of the present invention include microparticles manufactured by a process for producing granules by rotomelt granulation that comprises mixing bupropion hydrobromide 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-disk located within a vertical vessel having a bottom surface; wherein said rapidly rotating disk is located on the bottom surface of the vertical vessel wherein said gas is at a temperature sufficient to cause the bupropion hydrobromide to at least partially melt thereby causing said powdered materials to aggregate and form granules. Other embodiments of the present invention include microparticles manufactured by a process for producing granules 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 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 rotating disk is located on the bottom surface of the 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.

[0393] In rotomelt granulation, one of the feed powders must have a lower melting point than the 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 of the vessel. The powder is maintained in fluidized state by at least one stream of filtered air being circulated from the bottom of the vertical vessel through one or more inlets. The rotatable horizontal disk is then 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 3°C to 5°C below the melting point or melting range 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 of from 5 microns to 150 microns; and in certain embodiments have a diameter size in the range of 35 microns to 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 30°C; and in certain embodiments is below 100°C.

[0394] 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 of the binder particles become tacky. As the second powdered material of a smaller size is contacted with the tacky surface it forms a microlayer on the surface of the 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 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 materials can be varied to produce the desired granules.

[0395] In at least one embodiment of the present invention, bupropion hydrobromide is melted to act as a binding agent in the rotomelt granulation process. Examples of suitable excipients 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 10% w/w to 80% w/w; and in certain embodiments is in the range of from 30% w/w to 70% w/w of the powdered materials in the rotomelt granulation. The remaining weight percentage to provide a total of 100% w/w can be one or more suitable powdered pharmaceutical actives. Optionally the rotomelt granulation can also contain from 0% to 60% w/w of one or more powdered excipients wherein the total weight of all the powdered materials equals 100% w/w. The binder used in these embodiment of the invention can be a pharmaceutically acceptable dry powder having a particle size in the range of from 5 μm to 150 μm; and in certain embodiments in the range of from 35 μm to 80 μm. Suitable binders for rotomelt granulation are low melting point powdered binders, examples of which 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 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 30°C to 100°C; and in certain embodiments from 40°C to 85°C.

[0396] As a prophetic example of these embodiments that are manufactured by a rotomelt granulation process, 320g of bupropion hydrobromide and 80g PEG 8000 is dry blended and poured into a Glatt 1.1 chamber set-up as a rotary granulator with a longitudinal plate. Inlet air temperature is set to 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 900rpm. The product chamber temperature is raised to 60°C and then gradually reduced to 20°C over a period of approximately 20 minutes, during which spheronization is achieved.

[0397] Other embodiments of the invention involve the formation of a microparticle that has a core which includes bupropion hydrobromide and a compound which is sweet in taste and which has a negative heat of solution. 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 of sweetening compound used can depend on a number of factors including the size of the resulting microparticles, the size or volume of the resulting tablet, the sturdiness of the microparticle-coated microparticulant, the speed at which the tablet will disintegrate in the mouth, the degree of sweetness 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 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 80% of the weight of the resulting microparticles. The sweetener and 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 example: starch (for example, in an amount of from 5% to 10% as an aqueous paste); pregelatinized starch (for example, in an amount of 5% to 10% added dry to powder); gelatin (for example, in an amount of from 2% to 10% as an aqueous solution, or 2% in starch paste); polyvinylpyrrolidone (for example, in an amount of from 2% to 20% in an aqueous or alcoholic solution); methylcellulose (for example, in an amount of from 2% to 10% as an aqueous solution); sodium carboxy methylcellulose (for example, in an amount of from 2% to 10% as an aqueous solution); ethylcellulose (for example, in an amount of from 5% to 10% as an alcohol or hydroalcoholic solution); polyacrylamides (Polymer JR) (for example, in an amount of from 2% to 8% as an aqueous solution); polyvinyloxoazolidone (Devlex) (for example, in an amount of from 5% to 10% as an aqueous or hydroalcoholic solution); and polyvinyl alcohols (for example, in an amount of from 5% to 20% in aqueous solutions). Other adjuvants can also be used in forming

the core of the microparticles of the present embodiments of the invention, non-limiting examples of which include: calcium sulfate NF, Dibasic Calcium phosphate NF, Tribasic calcium sulfate NF, starch, calcium carbonate, microcrystalline cellulose, modified starches, lactose, sucrose and the like, Sta-Rx™, Avicel™, Solka-Floc™ BW40, alginic acid, Explotab™, AUTOTAB™, guar gum, kaolin Vecgum™, and bentonite. These adjuvants can be used in up to 20% w/w; and in certain embodiments are present in an amount of from 3% to 5% w/w.

[0398] As a prophetic example of these embodiments that have a core comprising bupropion hydrobromide and a compound which is sweet in taste, bupropion hydrobromide can be granulated using the following procedure: Polyvinylpyrrolidone K-30 USP (240.0 gm) is dissolved into distilled water (1,890.0 gm) with agitation. Mannitol powder USP (11,160 gm) and bupropion hydrobromide (600.0 gm) are placed in a Zanchetta 50-liter granulator/processor. After an initial two-minute dry mix of the powders with the chopper on and the propeller adjusted to 200 rpm, the polyvinylpyrrolidone K-30 solution is slowly sprayed into the mixing powder bed using an air-driven spray system. The total time of granulation including the time of solution addition is approximately eight minutes. The granulation end-point is determined visually and by the consistency of the resulting material. The material is then discharged onto trays and dried at 80°C utilizing supplied dry air for a period of six hours to a moisture content of not more than 0.08 percent. The dried material is then passed through a hammermill (knives forward) equipped with a U.S. #40 (420 micron) screen.

[0399] Other embodiments of this 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 of binding 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 primary function of the 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 function of the coating agent used in the actual coating step is to complete the final coating of each of the 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 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 hydroxypropylmethylcellulose (HPMC), or mixtures thereof. Among the acrylic polymers that can be advantageously chosen are the ammonio-methacrylate copolymer (Eudragit® RL or RS), the polyacrylate (Eudragit® NE) and the methacrylic acid copolymer (Eudragit® L or S), Eudragit® being a registered trademark of Rohm. In at leat one embodiment, the binder is of the same nature as the coating agent. To further accelerate the release of the bupropion hydrobromide, the coating suspension also comprises a permeabilizer which, on account of its intrinsic solubility properties, causes perforation of the membrane coating, thus allowing the bupropion hydrobromide to be released. Non-limiting examples of permeabilizers include povidone and its derivatives, polyethylene glycol, silica, polyols and low-viscosity cellulose polymers. Polymers of the type such as hypromellose, whose viscosity is equal to 6 centipoises, are used, for 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 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 of spraying of the mixture and the atomization pressure of said mixture. Thus, only some of the mixture of excipients is used during the granulation step, while the other portion can be used during the coating step. Thus, the rate of spraying of the coating suspension is higher during the granulation step than during the coating step, whereas the atomization pressure of the coating suspension is lower during the granulation step than during the coating step. In practice, at the laboratory scale in a fluidized-bed device, for example of the type such as Glatt GPCG1, during the granulation step, the rate of spraying of the coating suspension is

between 10 grams/minute and 25 grams/minute, and the atomization pressure is between 1 bar and 1.8 bar. During the coating step, the rate of spraying of the coating suspension is between 5 grams/minute and 15 grams/minute, while the atomization pressure is between 1.5 bar and 2.5 bar. In at least one embodiment, between 10% and 20% of the mixture of excipients is sprayed during the granulation step, the remainder being sprayed during the coating step.

[0400] 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 of immediate release, the microparticles can be manufactured according to the following process: A granulation solution is first prepared by dissolving 48 g of ethylcellulose in 273 g of ethyl alcohol. A coating suspension is then prepared by mixing 97 g of ethylcellulose, 28.5 g of polyethylene glycol 6000, 26 g of sodium croscarmellose, 10 g of precipitated silica and 27.5 g of aspartam in 1900 g of ethyl alcohol, until a homogeneous suspension is obtained. The powder mixture consisting of 700 grams of bupropion hydrobromide and 35 grams of Acdisol is then fluidized. The granulation is then started by spraying the granulation solution for 15 to 20 minutes at a spraying rate of 25 grams/minute and a suspension atomization pressure of 0.8 bar. The actual coating is then performed by spraying the coating suspension for 1 hour 30 minutes at a spraying rate of 15 to 20 grams/minute and a suspension spraying pressure of 1.5 bar.

[0401] Other embodiments of the invention involve coating the bupropion hydrobromide material, thereby forming a drug-containing microparticle. One such process for achieving this involves:

(i) Blending and fluidizing a powder mix of active principle and an adjuvant in order to obtain individual grains,

(ii) Separately liquifying under warm conditions a lipid matrix agent comprising either an ester of behenic acid and alcohol or an ester of palmitic/stearic acid and alcohol,

(iii) Coating the fluidized powder mix under warm conditions by spraying the lipid matrix agent over the individual grains,

(iv) Lowering the temperature of the combined product in order to allow the lipid matrix agent to solidify.

[0402] 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 of toxic residues in the final product. Furthermore, it is not necessary to carry out the quantitative determination of the traces of solvents, an analysis that can be very expensive. According to the process of this embodiment of the invention, the spraying conditions and thus the coating characteristics can be modified, in order to vary the release profile of bupropion hydrobromide, by varying several parameters, the adjustment characteristics of which remain simple. Thus, the spraying air pressure can be increased in order to promote the formation of a homogeneous film of lipid matrix agent around the grains. Advantageously, the rate of spraying of the 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 of the time, is obtained which can be low, corresponding to a slow release of the drug. Conversely, the spraying air pressure can be decreased in order to promote the agglomeration of the grains with one another. Advantageously, the rate of spraying of the lipid matrix agent can simultaneously be increased. In this case, a release profile of the grains obtained can be obtained which is high, corresponding to a rapid release of bupropion hydrobromide. In practice and according to the mass of powder employed, the value of the rate of spraying of the lipid matrix agent can be from two to four times higher when it is desired to promote the agglomeration of the 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 of the spraying air pressure can be from one to two times lower when it is desired to promote the agglomeration of the 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 of spraying air pressure and of spraying rate throughout the coating stage, making it possible to promote the formation of a homogeneous film around the grains or to promote the agglomeration of the grains. Once the sequence of the duration of the spraying air pressure and of the spraying rate has been determined, the coating operation can be carried out continuously and automatically. According to another characteristic of the process of manufacturing these embodiments, the temperature of the mixture of liquefied matrix agent and of spraying air is greater by 35°C to 60°C than the melting temperature of the lipid matrix agent. Likewise, the temperature of the fluidization air and that of the powder is approximately equal to the melting temperature of the lipid matrix agent, plus or minus 10°C. Furthermore, in order to obtain a

mixture of individual 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 spray technique, that is to say liquid spraying under pressure in the presence of compressed air. According to at least one embodiment, use is made of a powder comprising the drug and the adjuvant. In other words, after mixing and fluidizing the combined constituents of the powder, the lipid matrix agent is sprayed over the individual grains obtained. In order to avoid adhesion of the coated grains obtained, whether in the case where all the grains are treated or whether in the case where only a portion of the grains is treated, a stage of lubrication of the grains is inserted between the coating stage and the stage of putting into a pharmaceutical form. Furthermore, in order to obtain greater stability of the pharmaceutical composition, that is to say in order to minimize modifications relating to the release of the bupropion hydrobromide over time, the granules or tablets obtained in certain embodiments of this example can be subjected to a maturing stage in an oven, for at least 8 hours, at a temperature of between 45°C and 60°C; and in certain embodiments at 55°C.

[0403] As a prophetic example of these 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 of powder 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, sold under the trade name Compritol® 880 ATO) is liquefied separately at 120°C; the lipid matrix agent is sprayed over the heated powder mixture, and, finally, the temperature is lowered in order to allow the lipid matrix agent to solidify. These stages 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 of the grains, in accordance with the following table:

Parameters	**Batch 1**	**Batch 2**	**Batch 3**	**Batch 4**
% by weight of lipid matrix				
agent (Compritol® 888 ATO)	5	4	4	5
Fluidization air flow rate (m^3/h)	80	110	80	80
Agglomeration				

Atomization air pressure (bar)	2		1.5	1.5
Temperature of the powder bed (°C)	70		70	74
Spraying rate for Compritol® (g/min)	42		40	40
Coating				
Atomization air pressure (bar)	2.5	3.5	2	2
Temperature of the powder bed (°C)	70	66	71	70
Spraying rate for Compritol ® (g/min)	41	20	40	40

[0404] Another embodiment of the 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 selction of the appropriate polymer the microcrystals can possess diversified features such as gastroresistance and 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 of taste, gastroresistance and controlled release of the bupropion hydrobromide. In certain embodiments of this example, the following non-limiting list of polymers can be selected for coating of the bupropion hydrobromide in conventional fluidized based coating equipment: ethylcellulose (EC); hydroxypropylcellulose (HPC); hydroxypropylmethylcellulose (HPMC); gelatin; gelatin/acacia; gelatin/acacia/vinvylmethylether maleic anhydride; gelatin/acacia/ethylenemaleic anhydride; carboxymethyl cellulose; polyvinvylalcohol; cellulose acetate phthalate; nitrocellulose; shellac; wax; polymethacrylate polymers such as Eudragit® RS; Eudragit® RL or combinations of both, Eudragit® E and Eudragit NE30D; Kollicoat™ SR30D; and mixtures thereof.

Drug-Layered Microparticles

[0405] The drug-layered microparticles can be made by coating an inert particle or core, such as a non-pareil sphere (e.g. sugar sphere), with the bupropion salt and a polymeric binder. In certain embodiments of the 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 starch, salt or sugar spheres. The inert cores can have a

diameter ranging from 100 microns to 2000 microns. For example, in certain embodiments the diameter of the inert cores range from 150 microns to 1500 microns. In at least one embodiment, the inert cores are sugar spheres NF, containing not less than 62.5 % and not more than 91.5% of sucrose. 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 layer can be applied to the core prior to the application of the drug, polymeric binder, and any polymeric film layers. In at least one embodiment, the seal-coat layer does not substantially modify the release of the bupropion salt. Examples of suitable sealants that can be used in the seal-coat include permeable or soluble agents such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylcellulose, a polymethacrylate 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 of the sealant. Examples of such agents include talc, colloidal silica, polyvinyl alcohol, 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 of such seal-coats coatings are commercially available such as those sold under the Trade Marks Opadry® White Y-1-7000 and Opadry® OY/B/28920 White, each of which is available from Colorcon Limited, England.

[0406] The binding agent of these drug-layered embodiments is used to adhere the bupropion salt layer to the inert core or seal-coat of the core. In certain embodiments, the binding agent is water soluble, possesses sufficiently high adhesivity in order to adhere the bupropion salt layer to the inert core, and possesses an appropriate viscosity to provide substantial adhesion between the inert core and the bupropion 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 Kollidon VA64), hydroxyethylcellulose, low molecular weight hydroxypropylmethylcellulose (e.g. viscosity of 1-50 cps at 20oC; 2-12 cps at 20oC; or 4-6 cps at 20oC), hydroxypropylcellulose polymethacrylates, or mixtures thereof. For example, in certain

embodiments the composition of the binder for bupropion hydrobromide is from 1% to 25% w/w; in other embodiments from 2% to 10% w/w; and in still other embodiments from 3% to 5% w/w, expressed as a percentage of the total weight of the core.

[0407] Solvents can be used to apply the bupropion salt to the inert core, examples of which include lower alcohols such as ethanol, isopropanol and alcohol/water mixtures, acetone and chlorinated hydrocarbons.

[0408] The drug-layered microparticles can be prepared by forming a suspension or solution of the binder and the bupropion salt and then layering the suspension or solution on 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 effected 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 bupropion salt and achieve the desired dosage and release thereof upon in vivo administration.

[0409] In certain embodiments, the drug-layered microparticles can be manufactured using for example, the procedure in the following hypothetical experiment: Bupropion hydrobromide (2.8 kg) and hydroxypropyl methylcellulose (Methocel® E5) (0.40 kg) is dissolved in a mixture of water and isopropyl alcohol. The active drug solution can then be sprayed onto sugar spheres 30/35 (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 below 1%. The bupropion microparticles can then be passed through 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

[0410] The microparticles of the present invention can each be coated with at least one taste-masking 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.

[0411] In at least one embodiment, the taste-masking coating comprises a polymer such as ethylcellulose, which can be used as a dry polymer (such as Ethocel®, Dow Corning) solubilised in organic solvent prior to use, or as an aqueous dispersion. One commercially-available

aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® 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 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 Aquacoat is intimately mixed with a suitable plasticizer prior to use. Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). 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.

[0412] In other embodiments, polymethacrylate acrylic polymers can be employed as taste masking polymers. In at least one embodiment, the taste masking coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the tradename Eudragit® or from BASF under the tradename Kollicoat®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames Eudragit® RL and Eudragit® RS, respectively.

[0413] Eudragit® RL and Eudragit® RS are copolymers of acrylic and methacrylic esters 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 Eudragit® RL and 1:40 in Eudragit® RS. The mean molecular weight is 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® 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. Eudragit® RL/RS dispersions or solutions of the present invention can be mixed together in any desired ratio in order to ultimately obtain a taste masking coating having a desirable drug dissolution profile. Desirable formulations can be obtained, for example, from a coating derived from 100% Eudragit® RL; 50% Eudragit® RL with 50% Eudragit® RS; and 10% Eudragit® RL with 90% Eudragit® RS.

[0414] 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 (such as Eudragit® E, commercially available from Rohm Pharma). The hydrophobic acrylic polymer coatings of the present invention can further include a neutral copolymer based on poly (meth)acrylates, such as Eudragit® NE (NE=neutral ester), commercially available from Rohm Pharma. Eudragit® NE 30D lacquer films are insoluble in water and digestive fluids, but permeable and swellable.

[0415] In other embodiments, the taste masking polymer is a dispersion of poly (ethylacrylate, methyl methacrylate) 2:1 (Kollicoat® EMM 30 D, BASF).

[0416] In other embodiments, the taste masking polymer can be a polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as Kollicoat® SR30D (BASF).

[0417] Other taste masking polymers include hydroxypropylcellulose (HPC); hydroxypropylmethylcellulose (HPMC); hydroxyethylcellulose; gelatin; gelatin/acacia; gelatin/acacia/vinvylmethylether maleic anhydride; gelatin/acacia/ethylenemaleic anhydride; carboxymethyl cellulose; polyvinvylalcohol; nitrocellulose; polyvinylalcohol-polyethylene glycol graft-copolymers; shellac; wax and mixtures thereof.

[0418] The taste-masking coatings can be applied to the microparticles from one or more organic or 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 of the invention with a taste-masking coating include those conventionally used in pharmaceutical processing, such as fluidized bed 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 taste-masking coating.

[0419] In some embodiments a pore former can be included into the taste masking coat in order to influence the rate of release 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 and pores are formed that fill with the environmental fluid.

[0420] For example, the pore-formers of certain embodiments can comprise one or more water-soluble hydrophilic polymers in order to modify the release characteristics of the formulation. Examples of suitable hydrophilic polymers used as pore-formers include hydroxypropylmetlhylcellulose, cellulose ethers and protein-derived materials of these polymers, the cellulose ethers, especially 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, and sorbitol. In at least one embodiment, the hydrophilic polymer comprises hydroxypropyl-methylcellulose.

[0421] Other non-limiting examples of pore-formers include alkali metal salts such as lithium carbonate, sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium acetate, and sodium citrate. The pore-forming solids can also be polymers which are soluble in the environment of use, such as Carbowaxes™, and Carbopol™. In addition, the pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, and poly(a-w)alkylenediols. Other pore-formers which can be useful in the formulations of the 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, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, amylopectin, dextrin, etc., cross-linked polyvinylpyrrolidone, ion-exchange resins, such as potassium polymethacrylate, carrageenan, kappa-carrageenan, lambdacarrageenan, gum karaya, biosynthetic gum, etc. Other pore-formers include materials useful for making microporous lamina in the 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), polychloroethers, acetal polymers, polyesters 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, poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), and mixtures thereof.

[0422] In general, the amount of pore-former included in the taste masking coatings of certain embodiments of the present invention can be from 0.1% to 80%, by weight, 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 of the coated microparticle. In at least one embodiment that uses water soluble pore formers such as hydroxypropylmethylcellulose, a taste masking polymer: pore former dry weight ratio of between 10:1 and 1:1 can be present. In certain embodiments the taste masking polymer: pore former dry weight ratio is from 8:1 to 1.5:1; and in other embodiments from 6:1 to 2:1. In at least one embodiment using Eudragit® NE30D as the taste masking polymer and a hydroxypropylmethylcellulose (approx 5cps viscosity (in a 2% aqueous solution)) such as Methocel® E5, Pharmacoat 606G as the water soluble pore former, a taste masking polymer: pore former dry weight ratio ratio of 2:1 is present.

[0423] Colorants that can be used in the taste-masking coating include food, drug and cosmetic 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.

[0424] Flavorants that can be used in the taste-masking coating include natural and synthetic flavoring liquids. An illustrative list of such 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 of these 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, 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); mixtures thereof and the like.

[0425] 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); chloro 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-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.

[0426] The microparticle taste masking coat can also include one or more pharmaceutically acceptable excipients such as lubricants, emulsifiers, anti-foaming agents, plasticisers, solvents and the like.

[0427] Lubricants can be included to help reduce friction of coated microparticles during manufacturing. The lubricants that can be used in the taste masking coat of the 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, polyoxyethylene, glyceryl monostearate, 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. Compritol™), Stear-O-Wet™, Myvatex™ TL and mixtures thereof. In at least one embodiment, the lubricant is selected from magnesium stearate and talc. Combinations of these lubricants are operable. The lubricant can each be present in an amount of from 1% to 100% by weight of the polymer dry weight in the taste masking coat. For example, in certain embodiments wherein the taste masking polymer is Eudragit® NE30D or Eudragit® NE40D (Rohm America LLC) together with a hydrophilic pore former, the lubricant is present in an amount of from 1% to 30% by weight of the polymer dry weight; in other embodiments from 2% to 20%; and in still other embodiments at 10% by weight of the microparticle taste masking coat dry weight. In another embodiment where the taste masking polymer is ethylcellulose (Ethocel™ PR100, PR45, PR20, PR10 or PR7 polymer, or a mixture thereof), the lubricant can be present in an amount of from 10% to 100% by weight of the microparticle taste masking coat dry weight; in another embodiment from 20% to 80%; and in

still another embodiments at 50% by weight of the microparticle taste masking coat dry weight. In other embodiments, the taste masking coat does not include a pore former.

[0428] Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the microparticle taste masking coat to facilitate actual emulsification during manufacture of the coat, and also to ensure emulsion stability during the shelf-life of the product. Emulsifying agents useful for the microparticle taste masking coat composition 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 Span™ 80), and polysorbates (e.g. Tween™ 80). Combinations of emulsifying agents are operable. In at least one embodiment, the emulsifying agent is Tween™ 80. The emulsifying agent(s) can be present in an amount of from 0.01% to 5% by weight of the microparticle taste masking polymer dry weight. For example, in certain embodiments the emulsifying agent is present in an amount of from 0.05% to 3%; in other embodiments from 0.08% to 1.5%, and in still other embodiments at 0.1% by weight of the microparticle taste masking polymer dry weight.

[0429] Anti-foaming agent(s) can be included in the microparticle taste masking coat to reduce frothing or foaming during manufacture of the 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 0.1% to 10% of the microparticle taste masking coat weight. For example, in certain embodiments the anti-foaming agent is present in an amount of from 0.2% to 5%; in other embodiments from 0.3% to 1%, and in still other embodiments at 0.6% by weight of the microparticle taste masking polymer dry weight.

[0430] Plasticizer(s) can be included in the microparticle taste masking coat to provide increased flexibility and durability during manufacturing. Plasticisers that can be used in the microparticle taste masking coat 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 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 phthalate, diisononyl phthalate, 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-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, and mixtures thereof. The plasticizer can be present in an amount of from 1% to 80% of the taste masking polymer dry weight. For example, in certain embodiments the plasticizer is present in an amount of from 5% to 50%, in other embodiments from 10% to 40%, and in still other embodiments at 20% of the taste masking polymer dry weight.

[0431] The taste-masking coating can be present in an amount of from 1% to 90% by weight of the microparticle, depending upon the choice of polymer, the ratio of polymer:pore former, and the total surface area of the microparticle formulation. Since a certain thickness of taste masking coating has to be achieved in order to achieve effective taste masking, the amount of taste masking polymer coating used during manufacture is related to the total surface area of the batch of uncoated microparticles that requires a coating. The taste masking polymer surface area coverage can range from 0.5 mg/cm2 to 20mg/cm2. For example, in certain embodiments the surface area coverage of the taste masking polymer is from 0.6 mg/cm2 to 10mg/cm2, and in other embodiments is from 1 mg/cm2 to 5mg/cm2. In at least one embodiment of the invention, Eudragit® E is employed as the taste masking polymer at a surface area coverage of 4mg/cm2. One approach in estimating the total surface area of a multiparticulate batch is the permeability method according to Blaine (ASTM Des. C 205-55), which is based upon the mathematical model of laminar flow through capillaries arranged in parallel.

[0432] In the absence of an accuracte determination of total surface area of a microparticle, the amount of taste masking polymer to be applied can be expressed as a percentage of the uncoated microparticle. For example, in certain embodiments the taste-masking coating is present in an amount of from 5% to 60%; in other embodiments from 10% to 40%; and in still other embodiments from 15% to 35% by weight of the microparticle. In at least one embodiment the taste-masking coating is present in an amount of 30% by weight of the microparticle.

[0433] In certain embodiments, the diameter of the microparticles (with or without the taste-masking coating) range from 50 μm to 800 μm. For example, in certain embodiments the

diameter of the microparticles range from 100 μm to 600 μm, and in other embodiments from 150 μm to 450 μm.

Microparticle Control-Releasing Coat

[0434] The microparticles of the present invention can each be coated with at least one control-releasing coat. As used herein, the term "microparticle control-releasing coat" refers to the control-releasing coat that substantially surrounds each microparticle. The microparticle control-releasing coat is designed to achieve a controlled release of the bupropion salt from the microparticle. For example, the microparticle control-releasing 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 drug release in the duodenum. In another embodiment, the control releasing coat can be a delayed release coating that provides a delayed release of the bupropion salt with a predetermined lagtime that is independent of, or alternatively dependent on, the pH of the dissolution medium. For example, by increasing the thickness of the microparticle control-releasing coat using a pH independent diffusion polymer, lagtimes of 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, or 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 critical pH for the polymer of choice is exceeded. With either approach, following the predetermined lag, drug is released, for example within 1 hour for an immediate release pulse, or alternatively over a prolonged period of time, for example from 3 to 24 hours. In other embodiments, the microparticle control-releasing coat can provide a diffusion barrier that is independent of pH, thus facilitating a sustained release profile, with substantially full release of the bupropion salt occuring in from 3 to 24 hours following administration. In at least one embodiment, the microparticle control-releasing coat provides a delayed and sustained release of the bupropion salt from the microparticle with substantially full release in 24 hours following administration.

[0435] In certain embodiments, the microparticle control-releasing coat can provide substantially full release of the bupropion salt from the microparticle without requiring the use of any pore formers. Unneccessary pore formers that are not required in the microparticle control-releasing coat include hydrophilic polymers such as hydroxypropyl methylcellulose.

[0436] The microparticle control-releasing coat includes at least one polymer in an amount sufficient to achieve a controlled release of the bupropion salt. In at least one embodiment of the invention the control releasing 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, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid, methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid) (anhydride), glycidyl methacrylate copolymers, and mixtures thereof.

[0437] In at least one embodiment the control-releasing coat comprises polymerizable quaternary ammonium compounds, of which non-limiting examples include quaternized aminoalkyl esters and aminoalkyl amides of acrylic acid and methacrylic acid, for example β-methacryl-oxyethyl-trimethyl-ammonium methosulfate, β-acryloxy-propyl-trimethyl-ammonium chloride, and trimethylaminomethyl-methacrylamide methosulfate. The 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 styryltrialkyl ammonium salts. Other polymerizable quaternary ammonium compounds useful in the present invention include acryl- and methacryl-oxyethyltrimethyl-ammonium chloride and methosulfate, benzyldimethylammoniumethyl-methacrylate chloride, diethylmethylammoniumethyl-acrylate and -methacrylate methosulfate, N-trimethylammoniumpropylmethacrylamide chloride, and N-trimethylammonium-2,2-dimethylpropyl-1-methacrylate chloride.

[0438] In at least one embodiment, the polymer of the control-releasing coat is an acrylic polymer comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers (such as those sold under the Trade Mark Eudragit® 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 hydrobromide, it may be necessary in some embodiments to incorporate two or more ammonio methacrylate copolymers having differing

physical properties. For example, it is known that by changing the molar ratio of the quaternary ammonium groups to the neutral (meth)acrylic esters, the permeability properties of the resultant control-releasing coat can be modified.

[0439] In other embodiments of the 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. Such polymers are commercially available, e.g., from Rohm Pharma GmbH under the tradename Eudragit® L and Eudragit® S, and the ratio of free carboxyl groups to the esters is said to be 1:1 in Eudragit® L and 1:2 in Eudragit® S. Eudragit® L is insoluble in acids and pure water, but becomes increasingly permeable above pH 5.0. Eudragit® S is similar, except that it becomes increasingly 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 (such as Eudragit® E, commercially available from Rohm Pharma). The hydrophobic acrylic polymer coatings of certain embodiments can further include a neutral copolymer based on poly (meth)acrylates, such as Eudragit® NE (NE=neutral ester), commercially available from Rohm Pharma. Eudragit® NE 30D lacquer films are insoluble in water and digestive fluids, but permeable and swellable.

[0440] In other embodiments of the invention the control-releasing polymer is a dispersion of poly (ethylacrylate, methyl methacrylate) 2:1 (Kollicoat® EMM 30 D, BASF). In other embodiments the control releasing polymer can be a polyvinyl acetate stabilized with polyvinylpyrrolidone and sodium lauryl sulfate such as Kollicoat® SR30D (BASF). 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 compounds) in certain embodiments to the neutral (meth)acrylic esters, the permeability properties (and thus the dissolution profile) of the resultant coating can be modified.

[0441] In at least one embodiment the control releasing polymer is ethylcellulose, which can be used as a dry polmer (such as Ethocel®, Dow Corning) solubilised in organic solvent prior to use, or as an aqueous dispersion. One commercially available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® 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 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 Aquacoat® is intimately mixed with a suitable plasticizer prior to use. Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product can be prepared by incorporating a 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.

[0442] Other examples of polymers that can be used in the microparticle control-releasing coat include cellulose acetate phthalate, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium 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 of the polymer matrix, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (molecular weight 5k to 5000k), polyvinylpyrrolidone (molecular weight 10k to 360k), anionic and cationic hydrogels, zein, polyamides, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (molecular weight 30k to 300k), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, Polyox® polyethylene oxides (molecular weight 100k to 5000k), AquaKeep® acrylate polymers, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro cellulose, carboxymethyl cellulose, cellulose ethers, methyl ethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, cellulose butyrate, cellulose propionate,

gelatin, starch, maltodextrin, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol 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, scleroglucan and mixtures and blends thereof.

[0443] In at least one embodiment the control-releasing coat of the microparticles comprises polymers that can faciliatate mucoadhsion within the gastrointestinal tract. Non-limiting examples of polymers that can be used for mucoadhesion include carboxymethylcellulose, polyacrylic acid, Carbopol™, Polycarbophil™, gelatin and other natural or synthetic polymers.

[0444] In at least one embodiment the microparticles are coated with a control-releasing coat comprised of:

(i) at least one film-forming polymer which is insoluble in the liquids of the digestive tract, present in an amount of from 50% to 90% (e.g. from 50% to 80%) by weight of dry matter of the control-releasing coat composition, and including at least one non-hydrosoluble cellulose derivate, (e.g. ethylcellulose, cellulose acetate, or mixtures thereof);

(ii) at least one nitrogen-containing polymer, present in an amount of from 2% to 25% (e.g. from 5% to 15%) by weight of dry matter of the control-releasing coat composition, and including at least one polyacrylamide, poly-N-vinylaride, poly-N-vinyl-lactame, polyvinylpyrrolidone, or mixtures thereof;

(iii) optionally at least one plasticizer present in an amount of from 2% to 20% (e.g. from 4% to 15%) by weight of dry matter of the control-releasing coat composition, and including at least one of the following compounds: glycerol esters, phtalates, citrates, sebacates, cetylalcohol esters, castor oil, cutin, or mixtures thereof;

(iv) at least one surface-active and/or lubricating agent, present in an amount of from 2% to 20% (e.g. from 4% to 15%) by weight of dry matter of the control-releasing coat composition, and chosen from anionic surfactants such as the alkali metal and alkakine-earth metal salts of fatty acids, (e.g. stearic acid, oleic acid, and mixtures thereof), and/or from nonionic surfactants such as polyoxyethylenated esters of sorbitan, polyoxyethylenated esters of sorbitan, 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. sodium stearylfumarate, 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 5 hours; in certain embodiments at least 7 hours; and in certain other embodiments for a period of between 8 hours and 24 hours; so as to allow absorption of the bupropion hydrobromide during at least part of its time in the small intestine.

[0445] In a prophetic example of this embodiment of the invention, the microparticles are coated in a fluidized bead coater with the following coating solution:

Ethylcellulose	44.7g
PVP	4.8g
Castor oil	4.8g
Magnesium Stearate	6.1g
Acetone	479g
Isopranol	53g

[0446] In other embodiments of the 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 control-releasing coat, where the pore-formers can be inorganic or organic, and can include materials that can be dissolved, extracted or leached from the control-releasing coat in the environment of use. Upon exposure to fluids in the environment of use, the pore-formers are, for example, dissolved, and channels and pores are formed that fill with the environmental fluid. For example, the pore-formers can include one or more water-soluble hydrophilic polymers in order to modify the release characteristics of the formulation. Non-limiting examples of suitable hydrophilic polymers include hydroxypropylmetlhylcellulose, cellulose ethers and protein-derived materials of these polymers, the cellulose ethers, (e.g. hydroxyalkylcelluloses and carboxyalkylcelluloses), and mixtures thereof. Also, synthetic water-soluble polymers can be 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 of pore-formers 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 Carbowaxes®, Carbopol®, and the like. The possible pore-formers embrace diols, polyols, polyhydric alcohols, polyalkylene glycols, polyglycols, poly(a-w)alkylenediols, and mixtures thereof. Other pore-formers which can be useful in the formulations of the 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, arabinoglactin, pectin, tragacanth, scleroglucan, dextran, amylose, 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 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), polychloroethers, acetal polymers, polyesters 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, poly(urethane), cross-linked chain-extended poly(urethane), poly(imides), poly(benzimidazoles), collodion, regenerated proteins, semi-solid cross-linked poly(vinylpyrrolidone), and mixtures thereof.

[0447] In other embodiments a surfactant or an effervescent base can be included in the control-releasing coat, which can reduce and in certain embodiments overcome surface tension effects. In addition, the control-releasing coat of certain embodiments can include one or more 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 of the environmental fluid without causing the disruption of the

impermeable coating). The surfactants that can be used in the control-releasing coat of certain embodiments can be anionic, cationic, nonionic, or amphoteric. Non-limiting examples of such surfactants include sodium lauryl sulfate, sodium dodecyl sulfate, sorbitan esters, polysorbates, pluronics, potassium laurate, and mixtures thereof. Non-limiting examples of effervescent bases that can be used in the control-releasing coat of certain embodiments include sodium glycine carbonate, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, and mixtures thereof. Non-limiting examples of osmagents that can be used in the control-releasing coat of certain embodiments include sodium chloride, calcium chloride, calcium lactate, sodium sulfate, lactose, glucose, sucrose, mannitol, urea, other organic and inorganic compounds 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 25°C that is: greater than or equal to at least 10% by weight (wt/wt), greater than or equal to at least 15% by weight (wt/wt), or greater than or equal to at least 20% by weight (wt/wt). Non-limiting examples of swelling agents that can be used in the control-releasing coat of certain embodiments of the present invention include crosslinked polyvinylpyrrolidones (e.g. polyplasdone, crospovidone and mixtures thereof), crosslinked carboxyalkylcelluloses, crosslinked carboxymethylcellulose (e.g. 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: polyvinylpyrrolidone(s), polyalkylene oxides (e.g. polyethylene oxide, polypropylene oxide, and mixtures thereof), hydroxyalkylcelluloses (e.g. hydroxypropylcellulose, hydroxypropylmethylcellulose and mixtures thereof), 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. 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 of the swelling agent include the following sub-set of compounds: crosslinked polyvinylpyrrolidone (e.g. polyplasdone, crospovidone or mixtures thereof), crosslinked carboxyalkylcelluloses (e.g. crosslinked carboxymethylcelluloses 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 concentration of the swelling agent in the control-releasing coat of certain embodiments of the present invention can be from 3% to 40% by weight of the microparticle. For example, in certain embodiments the concentration of the swelling agent in the control-releasing coat is from 4% to 30%, and in other embodiments from 5% to 25% by weight of the microparticle.

[0448] In certain embodiments one or more pharmaceutically acceptable excipients consistent with the objects of the present invention can be used in the control-releasing coat, such as a lubricant, an emulsifying agent, an anti-foaming agent, and/or a plasticizer.

[0449] Lubricants can be included in the control-releasing coat to help reduce friction of coated microparticles during manufacturing. The lubricants that can be used in the control-releasing coat of certain embodiments of the 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, polyoxyethylene, glyceryl monostearate, 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, (e.g. Compritol™), Stear-O-Wet ™and Myvatex™ TL. In at least one embodiment, the lubricant is selected from magnesium stearate, talc and mixtures thereof. Combinations of these lubricants are operable. The lubricant can each be present in an amount of from 1% to 100% by weight of the control releasing coat dry weight. For example, in certain embodiments wherein the control release polymer is Eudragit® NE30D or Eudragit® NE40D (Rohm America LLC) together with a hydrophilic pore former, the lubricant is present in an amount of from 1% to 30% by weight of the control-releasing coat dry weight; in other embodiments from 2% to 20%; and in still other embodiments at 10% by weight of the microparticle control-releasing coat dry weight. In another embodiments where the control-release polymer is ethylcellulose (Ethocel™ PR100, PR45, PR20, PR10 or PR7 polymer, or a mixture thereof), the lubricant can be present in an amount of from 10% to 100% by weight of the microparticle control-releasing coat dry weight; in another embodiment from 20% to 80%; and in still another embodiments at 50% by weight of the microparticle control-releasing coat dry weight.

[0450] Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the microparticle control-releasing coat to facilitate actual emulsification during manufacture of the coat, and also to ensure emulsion stability during the shelf-life of the 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 as the polysaccharides, as well as glycerol esters, cellulose ethers, sorbitan esters (e.g. sorbitan monooleate or Span™ 80), and polysorbates (e.g. Tween™ 80). Combinations of emulsifying agents are operable. In at least one embodiment, the emulsifying agent is Tween™ 80. The emulsifying agent(s) can be present in an amount of from 0.01% to 5% by weight of the microparticle control releasing coat dry weight. For example, in certain embodiments the emulsifying agent is present in an amount of from 0.05% to 3%; in other embodiments from 0.08% to 1.5%, and in still other embodiments at 0.1% by weight of the microparticle control-releasing coat dry weight.

[0451] Anti-foaming agent(s) can be included in the microparticle control-releasing coat to reduce frothing or foaming during manufacture of the 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 Simethicone C. The anti-foaming agent can be present in an amount of from 0.1% to 10% of the microparticle control-releasing coat weight. For example, in certain embodiments the anti-foaming agent is present in an amount of from 0. 2% to 5%; in other embodiments from 0.3% to 1%, and in still other embodiments at 0.6% by weight of the microparticle control-releasing coat dry weight.

[0452] Plasticizer(s) can be included in the microparticle control-releasing coat to modify the properties and characteristics of the polymers used in the coat for convenient processing during manufacturing (e.g. provide increased flexibility and durability during manufacturing). 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 of the coat in the environment of use. During manufacture of the coat, the plasticizer can lower the melting temperature or glass transition temperature (softening point temperature) of the polymer or 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 of plasticisers that can be used in the microparticle control-releasing coat 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 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 phthalate, diisononyl phthalate, 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-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, diethyloxalate, diethylmalate, diethylfumerate, dibutylsuccinate, diethylmalonate, dibutylphthalate, dibutylsebacate, glyceroltributyrate, and mixtures thereof. The plasticizer can be present in an amount of from 1% to 80% of the control-releasing coat dry weight. For example, in certain embodiments the plasticizer is present in an amount of from 5% to 50%, in other embodiments from 10% to 40%, and in still other embodiments at 20% of the control-releasing coat dry weight.

[0453] The control releasing coat can be present in an amount of from 1% to 100% by weight of the microparticle, depending upon the choice of polymer, the ratio of polymer:pore former, and the total surface area of the microparticle formulation. Since a certain thickness of control 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 of the batch of uncoated microparticles that requires a coating. The control releasing polymer surface area coverage can range from 0.5 mg/cm2 to 30mg/cm2. For example in certain embodiments the surface area coverage of the control-releasing polymer is from 0.6 mg/cm2 to 20mg/cm2, and in other embodiments from 1 mg/cm2 to 5mg/cm2. In at least one embodiment of the invention, Eudragit® NE30D is used as the control releasing polymer at a surface area coverage of 10mg/cm2. One approach to estimate the total surface area of a multiparticulate batch is the permeability method according to Blaine (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 of total surface area of a microoarticle, the amount of control releasing polymer to be applied can be expressed as a percentage of the uncoated microparticle.

[0454] The control-releasing polymer can be present in an amount of from 1% to 99% by weight of the coated microparticle, depending on the controlled release profile desired. For example, in certain embodiments the polymer is present in an amount of from 5% to 80%, and in other

embodiments from 10% to 50% by weight of the coated microparticle. In at least one embodiment wherein the control-releasing polymer is Eudragit® NE30D, Eudragit® NE40D (Rohm America LLC), Kollicoat® SR 30D, or a mixture thereof, the polymer is present in an amount of from 1% to 50%; in other embodiments from 5% to 30%; and in still other embodiments is 15% by weight of the coated microparticle. In at least one embodiment wherein the control-releasing polymer is ethylcellulose, the polymer is present in an amount of from 1% to 99% by weight of the coated microparticle; in other embodiments from 5% to 50%; and in still other embodiments at 20% by weight of the coated microparticle. In at least one embodiment wherein the control-releasing polymer is Ethocel™, an ethyl cellulose grade PR100, PR45, PR20, PR10, PR7 polymer, or a mixture thereof, the polymer is present in an amount of from 5% to 30% by weight of the coated microparticle; in other embodiments from 10% to 25%; and in still other embodiments at 20% by weight of the coated microparticle

[0455] In certain embodiments, the diameter of the microparticles (with or without the control releasing coat) can range from 50 μm to 800 μm. For example, in certain embodiments the diameter of the microparticles range from 100 μm to 600 μm, and in other embodiments from 150 μm to 450 μm.

[0456] It is contemplated that in alternative embodiments, other excipients consistent with the objects of the present invention can also be used in the microparticle control-releasing coat.

[0457] In at least one embodiment, the microparticle control-releasing coat includes 96% Eudragit® NE30D, 1.9% Magnesium stearate, 1.9% Talc, 0.04% Tween 80, and 0.19% Simethicone C, when expressed as percentage by weight of the dry control-releasing coat composition. In another embodiment, the microparticle control-releasing coat includes 68% ethylcellulose, 17% glyceryl monostearate and 15% acetyl tributylcitrate when expressed as percentage by weight of the dry control-releasing coat composition.

[0458] The manufacturing process for the microparticle control-releasing coat can be as follows. Water is split into two portions of 15% and 85%. The anti-foaming agent and the emulsifying agent are then added to the 15% water portion, and mixed at 300 rpm to form portion A. In at least one embodiment, the anti-foaming agent is Simethicone C, and the emulsifying agent is Tween™ 80. A first lubricant is then added to the 85% water portion and mixed at 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 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 30 minutes at 500 rpm. In at least one embodiment, the aqueous dispersion of a neutral ester copolymer is Eudragit® NE30D. The resultant control-releasing coat solution can then be used to coat the microparticles to a 35% weight gain with the following parameters: An inlet temperature of from 10°C to 60°C, preferably from 20°C to 40°C, and more preferably from 25°C to 35°C; an outlet temperature of from 10°C to 60°C, preferably from 20°C to 40°C, and more preferably from 25°C to 35°C; a product temperature of from 10°C to 60°C, preferably from 15°C to 35°C, and more preferably from 22°C to 27°C; an air flow of from 10 c.m/h to 180 c.m/h, preferably from 40 c.m/h to 120 c.m/h, and more preferably from 60 c.m/h to 80 c.m/h; and an atomizing pressure of from 0.5 bar to 4.5 bar, preferably from 1 bar to 3 bar, and more preferably 2 bar. The resultant control-releasing coated microparticles can then be discharged from the coating chamber and ovencured with the following parameters: A curing temperature of from 20°C to 65°C, preferably from 30°C to 55°C, and more preferably 40°C; and a curing time of from 2 hours to 120 hours, preferably from 10 hours to 40 hours, and more preferably 24 hours. Any other technology resulting in the formulation of the microparticle control-releasing coat consistent with the objects of the invention can also be used.

3.2.4 Microparticle Dosage Forms

[0459] Highly useful dosage forms result when microparticles made from compositions containing a bupropion salt, spheronization aids, and other excipient(s) are coated with control-releasing polymer(s). The control-releasing 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 of the control-releasing coated multiparticles is not substantially affected by the compression of the 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 control-releasing coated microparticles. Alternatively, the coated microparticles can be filled into capsules.

[0460] The forms 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 of the 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 fact that such other solid oral dosage forms may be more difficult to commercially manufacture.

[0461] 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 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 of immediate release bupropion. The immediate release bupropion component can take the form of uncoated bupropion microparticles or powders; bupropion microparticles coated with a highly soluble immediate release coating, such as an Opadry® 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 placed in a capsule, or formed into a tablet. Examples of multiple component controlled release bupropion formulations are described in US 6,905,708.

3.2.5 Dose Sipping Technology

[0462] 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 of microparticles. In at least one embodiment, the drug formulation comprises bupropion hydrobromide. The system further comprises a fluid passing drug formulation retainer in the first end of the chamber. The retainer prevents release of the microparticles from the first end while permitting fluid entry into the chamber. In other embodiments, the microparticles contained within the chamber comprise bupropion hydrobroimde and at least one other drug.

[0463] The present invention further provides 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 drug delivery device has a first and second end. The first end of the 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 of the device to cause delivery of the fluid and microparticles of bupropion hydrobromide formulation into the patient's mouth.

[0464] The term "drug formulation retainer" as used herein, refers to a valve, plug or restriction, or the like that prevents passage of the 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 of fluids but does not allow for passage of other ingredients such as the drug formulation that is contained in the delivery device.

[0465] The dispensing device of this embodiment of the 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 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.

[0466] Generally the device is in prepared form prior to placement in a fluid. In at least one 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 of the opening is smaller than the plug. In at least one embodiment the restriction is made by crimping an end of the chamber. The second end of the chamber has a drug formulation retainer for preventing release of the plug. In at least one embodiment the retainer is prepared by crimping the end of the chamber. Microparticles of bupropion hydrobromide are then placed in the chamber. An end-cap is placed over the second end of the chamber prior to use to prevent release of the drug formulation. In prepared form, the plug substantially seals the first end of the chamber, thereby preventing loss of the drug formulation from the first end.

[0467] 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 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 of between 3 mm and 8 mm and a wall thickness of between 0.1 mm and 0.4 mm. The devices can be between 10 cm and 30 cm in length.

[0468] The fluid passing drug formulation retainer permits the free flow of liquid medium but prohibits passage of the drug formulation from the device prior to delivery. Where the retainer comprises a one-way plug or valve, the plug or valve will seal the straw 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 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 EthaFoam®. Other forms of one way plugs can be a balloon of elastomeric material, a one-way mechanical ball valve and the like.

[0469] Examples of fluid 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.

[0470] 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 0.21 inches and a length of 8 inches are heat sealed at one end. The seal is partially cut off so that the "one-way" plug cannot escape. The partially sealed end is enclosed by half of a size 1 hard gelatin capsule. Microparticles are then placed inside the open end of the straw. A "one-way" plug made of closed cell polyethylene foam, Microfoam® (DuPont) is trimmed to snugly fit inside the straw. The plug is then placed inside the straw, on top of the microparticles. During operation, the plug end of the straw is placed into a glass of water and the protective gelatin capsule on the top of the straw is removed. By slowly applying suction through the partially sealed end of the straw, the microparticles are sucked into the mouth and easily swallowed.

Osmotic Dosage Forms

[0471] Osmotic dosage forms, osmotic delivery devices, modified release osmotic dosage forms, or osmosis-controlled extended-release systems are terms used interchangeably herein and are defined to mean dosage forms which forcibly dispense the bupropion salt by pressure created by

osmosis or by osmosis and diffusion of fluid into a material which expands and forces the bupropion salt to be dispensed from the osmotic dosage form. Osmosis can be defined as the flow of solvent from a compartment with a low concentration of solute to a compartment with a high concentration of solute. The two compartments are separated by a membrane, wall, or coat, which allows flow of solvent (a liquid, aqueous media, or biological fluids) but not the solute. Examples of such membranes can for example be, a semipermeable membrane, microporous, asymmetric membrane, which asymmetric membrane can be permeable, semipermeable, perforated, or unperforated and can deliver the bupropion salt by osmotic pumping, diffusion or the combined mechanisms of diffusion and osmotic pumping. Thus, in principle, osmosis controlled release of the bupropion salt involves osmotic transport of an aqueous media into the osmotic dosage form followed by dissolution of the bupropion salt and the subsequent transport of the saturated solution of the bupropion salt by osmotic pumping of the solution through at least one passageway in the semipermeable membrane or by a combination of osmosis anddiffusion through the semipermeable membrane.

[0472] 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 of the bupropion salt used to form the core, the amount of pharmaceutically acceptable excipient used to form the core, the type of pharmaceutically 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 solutes, 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 used to form any coating, such as a control-releasing coating (e.g. a release slowing-coat) on the semipermeable membrane. 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 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released, when measured for example by using a USP Type 1 apparatus (Rotating Basket Method) in 900ml water, 0.1N HCl, 0.1N HCl + 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. Alternatively dissolution may be effected in USP-3 media such as SGF pH 1.2, Acetate Bufer at pH 4.5 or phosphate buffer at pH 6.8.

[0473] Osmotic devices also may be designed to achieve an in vitro release of no more than 40% after 2 hours, 40-75% release after 4 hours, at least 75% after 8 hours, and at least 85% after 16 hours when assayed using a dissolution medium such as identified above or known in the art.

[0474] In certain embodiments of the present invention, an osmotic dosage form is provided having a core comprising the bupropion 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.

[0475] In certain embodiments, the core of the osmotic dosage form comprises a water swellable polymer, non-limiting examples of which include hydroxypropyl cellulose, alkylcellulose, hydroxyalkylcellulose, polyalkylene oxide, polyethylene oxide, and mixtures thereof. A binder can be included in the core of certain embodiments of the osmotic dosage form to increase the core's mechanical strength. Non-limiting examples of binders include polyvinyl pyrollidine, carboxyvinyl polymer, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, a low molecular weight polyethylene oxide polymer, hydroxypropylmethylcellulose, dextrin, maltodextrin, gelatin, polyvinyl alcohol, xanthan gum, carbomers, caragheen, starch derivatives, and mixtures thereof. Lubricants can be included in certain embodiments of the 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 fumarate, hydrogenated vegetable oil, sodium benzoate, calcium stearate, and mixtures thereof. In other embodiments, additional inert excipients consistent with the objects of the invention can also be included in the core of the osmotic dosage form to facilitate the preparation and/or improve patient acceptability of the 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).

[0476] In at least one embodiment, the present invention comprises a modified release osmotic dosage form comprising bupropion hydrobromide present in a therapeutically effective amount which releases the bupropion hydrobromide by forcibly dispensing the bupropion hydrobromide

from a core via a 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 dispensed from the core of the dosage form, and (ii) is formulated such that the dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released.

[0477] In at least one embodiment, the modified release dosage form comprises an osmotic delivery device comprising a homogenous solid core comprising substantially the bupropion 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 salt from the core to the exterior of the dosage form through at least one passageway or by a combination of osmosis and diffusion such that the dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released, or afeter 2 hours no more than 40% is released, after 4 hours 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released..

[0478] 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 salt with at least one pharmaceutically acceptable excipient, said core of each microparticle surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery of the bupropion salt from the core to the exterior of the dosage form through a plurality of pores formed in the semipermeable membrane by inclusion of a pore forming agent in the membrane or by a combination ofosmosis and diffusion so as to allow communication of the core with the outside of the device for delivery of the bupropion salt and is formulated such that the dosage form comprises a therapeutically effective amount of the bupropion salt and

exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released. .

[0479] 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 salt in admixture with at least one pharmaceutically acceptable excipient, an osmagent and/or an osmopolymer, said core of each microparticle surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery of the bupropion salt from the core to the exterior of the dosage form through a plurality of 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 of the device for delivery of the bupropion salt and is formulated such that the dosage form comprises a therapeutically effective amount of the bupropion salt and exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0480] 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 salt with at least one pharmaceutically acceptable excipient in admixture with an osmagent, and/or an osmopolymer, and/or an absorption enhancer, said microparticles 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 of the bupropion salt from the tablet interior to the exterior of the dosage form through at least one passageway in the semipermeable membrane and/or by diffusion through the semipermeable membrane so as to

allow communication of the tablet interior with the exterior of the tablet for delivery of the bupropion salt and is formulated such that the dosage form comprises a therapeutically effective amount of the bupropion salt and exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released..

[0481] 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 salt with at least one pharmaceutically acceptable excipient, said at least one layer surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the layer and delivery of the bupropion salt from the layer to the exterior of the 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 of the core with the outside of the device for delivery of the bupropion salt and is formulated such that the dosage form comprises a therapeutically effective amount of the bupropion salt and exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released..

[0482] 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 salt in admixture with at least one pharmaceutically acceptable excipient, an osmagent and/or an osmopolymer, said at least one layer surrounded by a semipermeable membrane which permits entry of an aqueous liquid into the layer and delivery of the bupropion salt from the layer to the exterior of the 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 of the core

with the outside of the device for delivery of the bupropion salt and is formulated such that the dosage form comprises a therapeutically effective amount of the bupropion salt and exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released. or after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0483] 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 of the bupropion salt in admixture with an osmagent, and/or an osmopolymer, and/or and absorption enhancer, said core surrounded by a nontoxic wall, membrane or coat, such as for example a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery of the bupropion salt from the core to the exterior of the dosage form through at least one passageway in the semipermeable membrane and/or by diffusion through the membrane so as to allow communication of the core with the outside of the dosage form for delivery of the bupropion salt and is formulated such that the dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0484] In at least one embodiment the modified release dosage form comprises an osmotic delivery device comprising the bupropion 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 or coat, such as for example a semipermeable membrane which permits entry of an aqueous liquid into the core and delivery of the bupropion salt from the core to the exterior of the dosage form through at least one passageway in the semipermeable membrane or by osmosis and diffusion through the membrane so as to allow communication of the core with the outside of the dosage form for

delivery of the bupropion salt and is formulated such that the dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released; or a device wherein after 2 hours no more than 40% is released, after 4 hours 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released..

[0485] 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 therapeutically effective amount of the bupropion salt, and optionally at least one means for forcibly dispensing the bupropion salt from the device, said membrane comprising at least one means for the exit of the bupropion salt from the device, said device formulated such that when the device is in an aqueous medium, the bupropion salt, and optionally the at least one means for forcibly dispensing the bupropion salt from the device and the at least one means for the exit of the bupropion salt from the device cooperatively function to exhibit an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released; or a device wherein after 2 hours no more than 40% is released, after 4 hours nfrom 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0486] 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 therapeutically effective amount of the bupropion salt, at least one means for increasing the hydrostatic pressure inside the membrane and optionally at least one means for forcibly dispensing the bupropion salt from the device, said membrane comprising at least one means for the exit of the bupropion 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 salt from the device and the at least one means for the exit of the bupropion salt cooperatively function to exhibit an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion

salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released ; or a device wherein after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0487] In at least one embodiment the invention is directed to once-a-day bupropion hydrobromide sustained release formulations that is bioequivalent according to FDA guidelines to Wellbutrin™ ER or Zyban™/Wellbutrin™ SR when administered once-daily to a subject in need thereof and wherein the bupropion salt contained is more stable than the bupropion hydrochloride salt contained in Welbutrin ER or Zyban when stored at 40 degrees C and 75% relative humidity for at least 3, 4 5 and/or at least 6 months. Particularly, the invention encompasses bioequivalent 150 mg, 174 mg, 300 mg or 348 mg buropion HBr containing formulations.

[0488] In at least one embodiment the invention is directed to topical formulations containing bupropion hydrobromide that may be administered topically, e.g., transmucosally or transdermally. Particularly, the invention embraces topically administrable gels and patch type delivery devices which potentially may comprise another active agent such as nicotine.

[0489] In at least one embodiment the invention is directed to inhalable pulmonary deliverablecompositions containing bupropion hydrobromide that may be administered via pulmonary delivery to a subject in need thereof. Preferably, these compositions are produced according to the aerosol technology disclosed in US Patents 6,682,716; 6,716,415; 6,716,417; 6,783,753; 7,029,658; and 7,033,575 and others assigned to Alexza Corporation. These patents in particular disclose the use of such methods in producing aerosols containing anti-depressants for pulmonary delivery.

[0490] In at least one embodiment the invention is directed to injectable compositions comprising an effective amount of bupropion hydrobromide and a pharmaceuttically acceptable carrier or excipient.

[0491] In at least one embodiment, the invention is directed to a method of treating a condition comprising administering any one of the above described osmotic dosage forms to a patient in need of such administration once-daily.

[0492] The invention, in at least one embodiment, is directed to a method for administering a bupropion 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 salt, the modified release dosage form comprising an osmotic dosage form; and (b) administering the bupropion 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 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released; or a dosage form wherein after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0493] The invention, in at least one embodiment, is directed to a method for administering a bupropion 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 bupropion salt and optionally a means for forcibly dispensing the bupropion salt from the device, said membrane comprising at least one means for the exit of the bupropion salt from the dosage form, and (b) administering the bupropion salt from the dosage form which is formulated such that when the dosage form is in an aqueous medium, the bupropion salt and optionally the means for forcibly dispensing the bupropion salt and the at least one means for the exit of the bupropion salt cooperatively function to exhibit an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released; or a medicament wherein after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0494] The invention, in at least one embodiment, is directed to a method for administering a bupropion 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

bupropion salt, a means for increasing the hydrostatic pressure within the core and optionally a means for forcibly dispensing the bupropion salt from the device, said membrane comprising at least one means for the exit of the bupropion salt from the dosage form, and (b) administering the bupropion salt from the dosage form which is formulated such that when the dosage form is in an aqueous medium, the bupropion salt, the means for increasing the hydrostatic pressure within the core and optionally the means for forcibly dispensing the bupropion salt and the at least one means for the exit of the bupropion salt cooperatively function to exhibit an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released, or a device wherein after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0495] In at least one other embodiment, the osmotic dosage form further comprises an immediate release coat for the immediate release of the bupropion salt from the immediate release coat. In embodiments comprising the immediate release coat, the osmotic dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or a dosage form wherein after 2 hours no more than 40 % is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released or after 16 hours at least 85% is released.

[0496] 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 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or a dosage form wherein after 2 hours no

more than 40% is releaased, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0497] In at least one other embodiment, the osmotic dosage forms further comprise an osmotic subcoat. In embodiments comprising the osmotic subcoat, the osmotic dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or a dosage form wherein after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0498] In at least one other embodiment, the osmotic dosage forms further comprise a control-releasing coat. The control-releasing coat of the osmotic dosage form can, for example, control, extend, and/or delay the release of the bupropion salt. In embodiments comprising the control-releasing coat, the osmotic dosage form exhibits an in-vitro release rate such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released or a dosage form wherein after 2 hours no more than 40% is released, after 4 hours from 40-75% is released, after 8 hours at least 75% is released and after 16 hours at least 85% is released.

[0499] In at least one other embodiment, the control-releasing coat of the osmotic dosage form comprises a material that is soluble or 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.

[0500] In at least one embodiment, the control-releasing coat of the osmotic dosage form comprises at least one water-insoluble water-permeable film-forming polymer and at least one water-soluble polymer.

[0501] In at least one embodiment, the control-releasing coat of the osmotic dosage form comprises at least one water-insoluble water-permeable film-forming polymer and at least one water-soluble polymer and optionally at least one plasticizer.

[0502] In at least one embodiment, the control-releasing coat of the 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 of the bupropion salt from the core of the osmotic dosage form.

[0503] In at least one embodiment, the control-releasing coat of the 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.

[0504] In at least one embodiment, the control-releasing coat of the osmotic dosage form comprises at least one water-insoluble water-permeable film-forming polymer, at least one water-soluble polymer and at least one plasticizer.

[0505] In at least one embodiment, the control-releasing coat of the 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 salt from the core of the osmotic dosage form.

[0506] In at least one embodiment, the control-releasing coat of the 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.

[0507] In at least one embodiment, the control-releasing coat of the 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 55°C, one or more pharmaceutically acceptable excipients, and optionally at least one means for the exit of the bupropion salt form the core of the osmotic dosage form. This control-releasing coat is cured at a temperature at least equal to or greater than the melting point of the polyglycol.

[0508] In at least one other embodiment, the control-releasing coat of the osmotic dosage form comprises at least one enteric polymer.

[0509] The membrane or wall is permeable to the passage of aqueous media but not to the passage of the bupropion 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 salt by osmotic pumping,or the combined mechanisms of diffusion and osmotic pumping. The structural integrity of such membranes should remain substantially intact during the period of delivery of

the bupropion salt. By "substantially intact" it is meant that the semipermeable property of the membrane is not compromised during the period of delivery of the bupropion salt.

[0510] The semipermeable membrane of the osmotic dosage form 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 molecular weight of the at least one polymer or combination of polymers should be such that the polymer or combination of polymers is solid at the temperature of use i.e., both in-vitro and in-vivo.

[0511] In certain embodiments, the at least one polymer included in the semipermeable membrane of the osmotic dosage form can be a cellulose ester, such as for example, cellulose acetate, cellulose acetate acetoacetate, cellulose acetate benzoate, cellulose acetate butylsulfonate, cellulose acetate butyrate, cellulose acetate butyrate sulfate, cellulose acetate butyrate valerate. cellulose acetate caprate, cellulose acetate caproate, cellulose acetate caprylate, cellulose acetate carboxymethoxypropionate, cellulose acetate chloroacetate, cellulose acetate dimethaminoacetate, cellulose acetate dimethylaminoacetate, cellulose acetate dimethylsulfamate, cellulose acetate dipalmitate, cellulose acetate dipropylsulfamate, cellulose acetate ethoxyacetate, cellulose acetate ethyl carbamate, cellulose acetate ethyl 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 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, cellulose dipentanlate, cellulose formate, cellulose methacrylates, cellulose methoxybenzoate, cellulose nitrate, cellulose nitrobenzoate, 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, cellulose triformate, cellulose triheptanoate, cellulose triheptylate, cellulose trilaurate, cellulose trimyristate, cellulose trinitrate, cellulose trioctanoate, cellulose tripalmitate, cellulose tripropionate, cellulose trisuccinate, cellulose trivalerate, cellulose valerate palmitate; a cellulose ether, such as for example, 2-cyanoethyl cellulose, 2-hydroxybutyl methyl cellulose, 2-hydroxyethyl cellulose, 2-hydroxyethyl ethyl cellulose, 2-hydroxyethyl methyl cellulose, 2-hydroxypropyl cellulose, 2-hydroxypropyl methyl cellulose, dimethoxyethyl cellulose acetate, ethyl 2-hydroxylethyl cellulose, ethyl cellulose, ethyl cellulose sulfate, ethylcellulose dimethylsulfamate, methyl cellulose, methyl cellulose acetate, methylcyanoethyl cellulose, sodium carboxymethyl 2-hydroxyethyl cellulose, sodium carboxymethyl cellulose; a polysulfone, such as for example, polyethersulfones; a polycarbonate; a polyurethane; a polyvinyl acetate; a polyvinyl alcohol; a polyester; a polyalkene such as polyethylene, ethylene vinyl alcohol copolymer, polypropylene, poly(1,2-dimethyl-1-butenylene), poly(1-bromo-1-butenylene), poly(1, butene), poly(1-chloro-1-butenylene), poly(1-decyl-1-butenylene), poly(1-hexane), poly(1-isopropyl-1-butenylene), poly(1-pentene), poly(3-vinylpyrene), poly(4-methoxyl 1-butenylene), poly(ethylene-co-methyl styrene), poly vinyl-chloride, poly(ethylene-co-tetrafluoroethylene), poly(ethylene-terephthalate), poly(dodecafluorobutoxylethylene), poly(hexafluoroprolylene), poly(hexyloxyethylene), poly(isobutene), poly(isobutene-co-isoprene), poly(isoprene), poly-butadiene, poly[(pentafluoroethyl)ethylene], poly[2-ethylhexyloxy)ethylene], poly(butylethylene), poly(tertbutylethylene), poly(cylclohexylethylene), poly[(cyclohexylmethyl)ethylene], poly(cyclopentylethylene), poly(decylethylene), poly-(dodecy-lethylene), poly(neopentylethylene), poly(propylethylene); a polystyrene, such as for example, poly(2,4-dimethyl styrene), poly(3-methyl styrene), poly(4-methoxystyrene), 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(chloroprene), poly(cyclohexloxyethylene), poly(decyloxyethylene), poly(dichloroethylene), poly(difluoroethylene), poly(vinyl acetate), poly(vinyltrimethyilstyrene); a polysiloxane, such as for example, poly(dimethylsiloxane); a polyacrylic acid derivative, such as for example, polyacrylates, polymethyl methacrylate, poly(acrylic acid) higher alkyl esters, poly(ethylmethacrylate), poly(hexadecyl methacrylate-co-methylmethacrylate), poly-(methylacrylate-co-styrene), poly(n-butyl methacrylate), poly(n-butyl-acrylate), poly (cyclododecyl acrylate), poly(benzyl acrylate), poly(butylacrylate), 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), poly(octyl methacrylate), acrylic resins; a polyamide, such as for example, poly(iminoadipoyliminododecamethylene), poly(iminoadipoyliminohexamethylene), polyethers, such as for example, poly(octyloxyethylene), poly(oxyphenylethylene), poly(oxypropylene), poly(pentyloxyethylene), poly(phenoxy styrene), poly(secbutroxylethylene), poly(tert-butoxyethylene); and combinations thereof.

[0512] In at least one embodiment, the at least one wax included in the semipermeable membrane of 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 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, petroleum ceresin, 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.

[0513] In at least one embodiment, the semipermeable membrane of the osmotic dosage form can comprise a combination of at least one polymer, wax, or combinations thereof and optionally at least one excipient. The total weight percent of all components comprising the semipermeable membrane is 100%.

[0514] In embodiments where the bupropion salt is released through the membrane or wall in a controlled manner by the combined mechanisms of diffusion and osmotic pumping, the membrane or wall can comprise at least one of the above described polymers and/or waxes or a combination of polymers, such as for example, cellulose esters, copolymers of methacrylate salts and optionally a plasticizer.

[0515] The poly(methacrylate) copolymer salts used in the manufacturing of the membrane for the 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(ammonium methacrylate) copolymer RL (Eudragit®RL), poly(ammonium methacrylate) copolymer (type A-USP/NF), poly(aminoalkyl methacrylate) copolymer RL-JSP I), and (ethyl acrylate)-(methyl methacrylate)-[(trimethylammonium)-ethylmethacrylate] (1:2:0.2) copolymer, MW 150,000. Other examples of such copolymers include those available from Rohm Pharma, Weiterstadt, such as for example, Eudragit®RS 100: solid polymer, Eudragit®RL 12.5:12.5% solution in solvent, Eudragit®RL 30 D: 30% aqueous dispersion, and other equivalent products. The following poly (ammonium methacrylate) copolymers can also be used: ammonium methacrylate copolymer RS (Eudragit®RS), poly(ammonium methacrylate) copolymer (type B-USP/NF), poly(aminoalkyl methacrylate) copolymer (RSL-JSP I), (ethyl acrylate)-(methyl methacrylate)-[(trimethylammonium)-ethyl methacrylate] (1:2:0.1) copolymer, PM 150,000. Specific polymers include (Rohm Pharma, Weiterstadt): Eudragit®RS 100: solid polymer, Eudragit®RS 12.5: 12.5% solution in solvent, Eudragit®RS 30 D: 30% aqueous dispersion and other equivalent products. RL is readily water permeable while Eudragit®RS is hardly water permeable. By employing mixtures of both Eudragit®RL and Eudragit®RS, membranes having the desired degree of permeability to achieve the in-vitro dissolution rates and in-vivo pharmacokinetic parameters can be prepared.

[0516] The use of plasticizers is optional but can be included in the osmotic dosage forms to modify the properties and characteristics of the polymers used in the coats or core of the osmotic dosage forms for convenient processing during manufacture of the coats and/or the core of the osmotic dosage forms if necessary. As used herein, the term "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 of the coat(s) and/or the core of the osmotic dosage form in the environment of use. During manufacture of the coat, the plasticizer should be able to lower the melting temperature or glass transition temperature (softening point temperature) of the polymer or binder. Plasticizers, such as low molecular weight PEG, generally broaden the average molecular weight of a polymer in which they are included thereby lowering 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.

[0517] Plasticizers useful in the osmotic dosage form of the invention can include, for example, low molecular weight polymers, oligomers, copolymers, oils, small organic molecules, low molecular weight polyols 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, triacetin, propylene glycol, glycerin, ethylene glycol, 1,2-butylene glycol, 2,3-butylene glycol, styrene glycol, diethylene 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, acetyltributylcitrate, triethyl citrate, acetyl triethyl citrate, tributyl citrate and allyl glycolate. All such plasticizers are commercially available from sources such as Aldrich or Sigma Chemical Co. It is also contemplated and within the scope of the 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 of methods, such as 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 hydrophilicity of the coat(s) and/or the core of the osmotic dosage form in the environment of use may it be in-vitro or in-vivo. Accordingly, certain plasticizers can function as flux enhancers.

[0518] The ratio of cellulose esters:copolymers of methacrylate salts:plasticizer of the osmotic dosage forms can be, for example, from 1-99% of the cellulose ester by weight:84-0.5% of the copolymers of methacrylate salt by weight:15-0.5% of the plasticizer by weight. The total weight percent of all components comprising the wall is 100%.

[0519] Aside from the semipermeable membranes of the osmotic dosage form described above, asymmetric membranes can also be used to surround the core of an osmotic dosage form for the controlled release of the bupropion 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 salt by osmotic pumping, diffusion or the combined mechanisms of diffusion and osmotic pumping. The reader is referred to US Patent No. 5,612,059 for the manufacture and use thereof of asymmetric membranes for the

controlled-release of an active through one or more asymmetric membranes by osmosis or by a combination of diffusion osmotic pumping.

[0520] In certain embodiments of the osmotic dosage form, the semipermeable membrane can further comprise a flux enhancing, or channeling agent.

[0521] "Flux enhancing agents" or "channeling agents" are any materials which function to increase the volume of fluid imbibed into the core to enable the osmotic dosage form to dispense substantially all of the bupropion salt through at least one passageway in the semipermeable membrane by osmosis or by osmosis and by diffusion through the semipermeable membrane. The flux enhancing agent dissolves to form paths in the semipermeable membrane for the fluid to enter the core and dissolve the bupropion salt in the core together with the osmagent, if one is present, but does not allow exist of the bupropion salt. The flux enhancing agent can be any water soluble material or an enteric material which allows an increase in the volume of liquid imbibed into the core but does not allow for the exit of the bupropion salt. Such materials can be, for example, sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose 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 of the osmotic dosage form. Flux enhancers or channeling agents can also function as a means for the exit of the bupropion salt from the core if the flux enhancing or channeling agent is used in a sufficient amount.

[0522] The expression "passageway" as used herein comprises means and methods suitable for the metered release of the bupropion salt from the core of the osmotic dosage form. The means for the exit of the bupropion salt comprises at least one passageway, including orifice, bore, aperture, pore, porous element, hollow fiber, capillary tube, porous overlay, or porous element that provides for the osmotic controlled release of the bupropion salt. The means for the exit can be linear or tortuous. The means for the exit includes a weakened area of the semipermeable membrane or a material that erodes or is leached from the wall in a fluid environment of use to produce at least one dimensioned passageway. The means for the exit of the bupropion salt can comprise any leachable material, which when leaches out of the semipermeable membrane forms a passageway suitable for the exit of the bupropion 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 filament, poly(vinyl alcohol), leachable polysaccharides, salts, oxides, sorbitol, or sucrose. 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 of the bupropion salt from the dosage form. The dimensions of the means of the exit for the bupropion salt is sized such so as to allow the bupropion 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 of the wall.

[0523] 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 e.g., by mechanical means after the semipermeable membrane is applied to the core of 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 of the bupropion salt, such as for example a cylindrical or frustoconical pin which is integral with the inside surface of the upper punch of a punch used to form the osmotic dosage form. Alternatively, the means for the exit of the bupropion 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 osmotic dosage form. The means for the exit of the bupropion 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 of the bupropion salt including two, three, four, five, six seven, eight, nine ten or more exit means and can be formed in any place of the osmotic dosage form. The various positions of the means for the exit are disclosed, for example, in U.S. Pat. No. 6,491,949. The type, number, and dimension(s) of the means for the exit of the bupropion 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 the pharmaceutical delivery arts. The means for the exit and equipment for forming the means for the exit are disclosed for example in U.S. Pat. Nos. 3,845,770; 3,916,899; 4,034,758; 4,063,064; 4,077,407, 4,088,864; 4,200,098; 4,285,987; 4,783,337; 4,816,263; and 5,071,607.

[0524] The osmotic device can further comprise a control-releasing coat surrounding the semipermeable membrane comprising an enteric or delayed release coat that is soluble or 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), hydroxypropyl methylcellulose phthalate (HP), poly(methacrylate ethylacrylate) (1:1) copolymer (MA-EA), poly(methacrylate methylmethacrylate) (1:1) copolymer (MA-MMA), poly(methacrylate methylmethacrylate) (1:2) copolymer, Eudragit® L-30-D (MA-EA, 1:1), Eudragit® L-100-55 (MA-EA, 1:1), hyciroxypropyl methylcellulose acetate succinate (HPMCAS), Coateric® (PVAP), Aquateric® (CAP), AQUACOAT® (HPMCAS) and combinations thereof. The enteric coat can also comprise dissolution aids, stability modifiers, and bioabsorption enhancers.

[0525] When the control-releasing coat of osmotic dosage forms of the present invention is intended to be dissolved, eroded or become detached from the osmotic dosage form, materials such as hydroxypropylcellulose, microcrystalline cellulose (MCC, Avicel™ from FMC Corp.), poly (ethylene-vinyl acetate) (60:40) copolymer (EVAC from Aldrich Chemical Co.), 2-hydroxyethylmethacrylate (HEMA), MMA, terpolymers of HEMA: MMA:MA synthesized in the presence of N,N'-bis(methacryloyloxyethyloxycarbonylamino)-azobenzene, azopolymers, enteric coated timed release system (Time Clock® from Pharmaceutical Profiles, Ltd., UK) and calcium pectinate can be used.

[0526] Polymers for use in the control-releasing coat of osmotic dosage forms of the present invention can be, for example, enteric materials that resist the action of gastric fluid avoiding permeation through the semipermeable wall while one or more of the materials in the core of the dosage form are solubilized in the intestinal tract thereby allowing delivery of the bupropion salt in the core by osmotic pumping in the osmotic dosage form to begin. A material that adapts to this kind of requirement can be, for example, a poly(vinylpyrrolidone)-vinyl acetate copolymer, such as the material supplied by BASF under its Kollidon® VA64 trademark, mixed with magnesium stearate and other similar excipients. The enteric coat can also comprise povidone, which is supplied by BASF under its Kollidon® K 30 trademark, and hydroxypropyl methylcellulose, which is supplied by Dow under its Methocel® E-15 trademark. The materials

can be prepared in solutions having different concentrations of polymer according to the desired solution viscosity. For example, a 10% P/V aqueous solution of Kollidon® K 30 has a viscosity of 5.5-8.5 cps at 20°C, and a 2% P/V aqueous solution of Methocel® E-15 has a viscosity of 13-18 cps at 20°C.

[0527] The control-releasing coat of osmotic dosage forms of the present invention can comprise one or more materials that do not dissolve, disintegrate, or change their structural integrity in the stomach and during the period of time that the tablet resides in the stomach, such as for example a member chosen from the group (a) keratin, keratin saridarac-tolu, salol (phenyl salicylate), salol beta-naphthylbenzoate and acetotannin, 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 of formalized protein, formalized gelatin, and formalized cross-linked gelatin and exchange resins; (c) a member chosen from the group of myristic acid-hydrogenated castor oil-cholesterol, stearic acid-mutton tallow, stearic acid-balsam of tolu, and stearic acid-castor oil; (d) a member chosen from the group of shellac, ammoniated shellac, ammoniated shellac-salol, shellac-wool fat, shellac-acetyl alcohol, shellac-stearic acid-balsam of tolu, and shellac n-butyl stearate; (e) a member chosen from the group of abietic acid, methyl abictate, benzoin, balsam of tolu, sandarac, mastic with tolu, and mastic with tolu, and mastic with acetyl alcohol; (f) acrylic resins represented by anionic polymers synthesized from methacrylate acid and methacrylic acid methyl ester, copolymeric acrylic resins of methacrylic and methacrylic acid and methacrylic acid alkyl esters, copolymers of alkacrylic acid and alkacrylic acid alkyl esters, acrylic resins such as dimethylaminoethylmethacrylate-butylmethacrylate-methylmethacrylate copolymer of 150,000 molecular weight, methacrylic acid-methylmethacrylate 50:50 copolymer of 135,000 molecular weight, methacrylic acid-methylmethacrylate-30:70-copolymer of 135,000 mol. wt., methacrylic acid-dimethylaminoethyl-methacrylate-ethylacrylate of 750,000 mol. wt., methacrylic acid-methylmethacrylate-ethylacrylate of 1,000,000 mol. wt., and ethylacrylate-methylmethacrylate-ethylacrylate of 550,000 mol. 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 phthalate, methylcellulose 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 methylcellulose phthalate, cellulose acetate hexahydrophthalate, hydroxypropyl methylcellulose hexahydrophthalate, polyvinyl acetate phthalate diethyl phthalate, dibutyl phthalate, dialkyl phthalate wherein the alkyl comprises from 1 to 7 straight and branched alkyl groups, aryl phthalates, and other materials known to one or ordinary skill in the art.

[0528] Accordingly, in at least one other embodiment, the control-releasing coat of osmotic dosage forms of the present invention comprises a water-insoluble water-permeable film-forming polymer, water-soluble polymer, and optionally a plasticizer and/or a pore-forming agent. The water-insoluble, water-permeable film-forming polymers useful for the manufacture of the control-releasing coat can be cellulose ethers, such as for example, ethyl celluloses chosen from the group of ethyl cellulose grade PR100, ethyl cellulose grade PR20 and any combination thereof; cellulose esters, and polyvinyl alcohol. The water-soluble polymers useful for the control-releasing coat can be, for example, polyvinylpyrrolidone, hydroxypropyl methylcellulose and hydroxypropyl cellulose.

[0529] The skilled artisan will appreciate that that the desired in-vitro release rates described herein for the bupropion salt can be achieved by controlling the permeability and/or the amount of coating applied to the core of the osmotic dosage form. The permeability of the control-releasing coat, can be altered by varying the ratio of the water-insoluble, water-permeable film-forming polymer:water-soluble polymer:optionally the plasticizer and/or the quantity of coating applied to the core of the osmotic dosage form. A more extended release is generally obtained with a higher amount of water-insoluble, water-permeable film forming polymer. The addition of other excipients to the core of the osmotic dosage form can also alter the permeability of the control-releasing coat. For example, if the core of the osmotic dosage form comprises a swellable polymer, the amount of plasticizer in the control-releasing 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 of the water-insoluble water-permeable film forming polymer and water-soluble polymer may also be altered depending on whether a faster or slower in-vitro dissolution is desired.

[0530] In at least one other embodiment, the control-releasing coat of the 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 55°C, and one or more pharmaceutically

acceptable excipients and cured at a temperature at least equal to or greater than the melting point of the poly glycol. The manufacture and use of such coating formulations are described in detail in US published patent application 20040037883A1, published on February 26, 2004. In brief, examples of neutral ester copolymers without any functional groups comprising the coat can be Eudragit® NE30D, Eudragit® NE40D (Röhm America LLC), or mixtures thereof. This coat can comprise hydrophilic agents to promote wetting of the coat when in contact with gastrointestinal fluids. Such hydrophilic agents include, for example, hydrophilic water-soluble polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) and combinations thereof. The poly glycol can be, for example, chosen from the group of polyethylene glycol 6000, polyethylene glycol 8000, polyethylene glycol 10000, polyethylene glycol 20000, Poloxamer 188, Poloxamer 338, Poloxamer 407, Polyethylene Oxides, Polyoxyethylene Alkyl Ethers, and Polyoxyethylene Stearates, and combinations thereof. This control-releasing coat of the osmotic dosage form can further comprise a pore-forming agent. The pore former, however, must be sufficiently insoluble in the aqueous dispersion, but must be sufficiently soluble in the environment of use. One method for producing such coats is detailed in European patent EP 1267842B1.

[0531] The control-releasing coat of certain embodiments of the osmotic dosage form of certain embodiments of the present invention includes at least one polymer in an amount sufficient to achieve a controlled release of the bupropion salt. Examples of polymers that can be used in the control-releasing coat of these embodiments include cellulose acetate phthalate, cellulose acetate trimaletate, hydroxy propyl methylcellulose phthalate, polyvinyl acetate phthalate, ammonio methacrylate copolymers such as those sold under the Trade Mark Eudragit® RS and RL, poly acrylic acid and poly acrylate and methacrylate copolymers such as those sold under the trademark Eudragit® S and L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, shellac; hydrogels and gel-forming materials, such as carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium carmellose, 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 methylcellulose, polyvinylpyrrolidone, crosslinked starch, microcrystalline cellulose, chitin, aminoacryl-methacrylate copolymer (Eudragit® RS-PM, Rohm & Haas),

pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (molecular weight 5K-5000K), polyvinylpyrrolidone (molecular weight 10K-360K), anionic and cationic hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (molecular weight 30K-300K), polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, polyacrylamides, Polyox® polyethylene oxides (molecular weight 100K-5000K), AquaKeep® acrylate polymers, diesters of polyglucan, crosslinked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, sodium starch glycolate (e.g. Explotab®; Edward Mandell C. Ltd.); hydrophilic polymers such as polysaccharides, methyl cellulose, sodium or calcium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitro cellulose, carboxymethyl cellulose, cellulose ethers, polyethylene oxides (e.g. Polyox®, Union Carbide), methyl ethyl cellulose, ethylhydroxy 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 of methacrylic acid or methacrylic acid (e.g. Eudragit®, Rohm and Haas), 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, scleroglucan and mixtures and blends thereof. In at least one embodiment of the osmotic dosage form of the present invention, the polymer is an acrylate dispersion such as Eudragit® NE30D, Eudragit® NE40D (Rohm America LLC), Kollicoat® SR 30D, Surelease®, or a mixture thereof. The polymer can be present in an amount of from 20% to 90% by weight of the control-releasing coat, depending on the controlled release profile desired. For example, in certain embodiments of the osmotic dosage form, the polymer is present in an amount of from 50% to 95%, in other embodiments from 60% to 90%, and in still other embodiments 75% of the control-releasing coat weight.

[0532] The control-releasing coat of certain embodiments of the osmotic dosage form of the present invention can also include one or more pharmaceutically acceptable excipients such as lubricants, emulsifiers, anti-foaming agents, plasticisers, solvents and the like.

[0533] Lubricants can be included in the control-releasing coat of certain embodiments of the osmotic dosage form of the present invention to help reduce friction of coated microparticles during manufacturing. The lubricants that can be used in the control-releasing 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 fumarate, light mineral oil, waxy fatty acid esters such as glyceryl behenate, (i.e. CompritolTM), Stear-O-WetTM and MyvatexTM TL. In at least one embodiment, the lubricant is selected from magnesium stearate and talc. Combinations of these lubricants are operable. The lubricant(s) can each be present in an amount of from 0.1% to 80% of the control-releasing coat weight. For example, in certain embodiments the lubricant is present in an amount of from 0.5% to 20%, in other embodiments from 0.8% to 10%, and in still other embodiments 1.5% of the control-releasing coat weight.

[0534] Emulsifying agent(s) (also called emulsifiers or emulgents) can be included in the control-releasing coat of the osmotic dosage forms of certain embodiments of the present invention to facilitate actual emulsification during manufacture of the coat, and also to increase or ensure emulsion stability during the shelf-life of the product. Emulsifying agents useful for the control-releasing 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 Span™ 80), and polysorbates (e.g. Tween™ 80). Combinations of emulsifying agents are operable. The emulsifying agent(s) can be present in an amount of from 0.01% to 0.25% of the control-releasing coat weight. For example, in certain embodiments the emulsifying agent is present in an amount of from 0.01% to 0.15%, in other embodiments from 0.01% to 0.07%, and in still other embodiments 0.03% of the control-releasing coat weight.

[0535] Anti-foaming agent(s) can be included in the control-releasing coat of the osmotic dosage form of certain embodiments of the present invention to reduce frothing or foaming during manufacture of the coat. Anti-foaming agents useful for the control-releasing coat composition of the osmotic dosage form include, but are not liminted to simethicone, polyglycol and silicon oil. In at least one embodiment the anti-foaming agent is Simethicone C. The anti-foaming agent can be present in an amount of from 0.01% to 10% of the control-releasing coat weight.

For example, in certain embodiments the anti-foaming agnet is present in an amount of from 0.05% to 1%, in other embodiments from 0.1% to 0.3%, and in still other embodiments 0.15% of the control-releasing coat weight.

[0536] It is contemplated that in certain embodiments, other excipients consistent with the objects of the present invention can also be used in the control-releasing coat of the osmotic dosage form.

[0537] In at least one embodiment, the control-releasing coat of the osmotic dosage form includes 75% Eudragit® NE30D, 1.5% Magnesium stearate, 1.5% Talc, 0.03% Tween™ 80, 0.15% Simethicone C, and 21.82% water, by weight of the control-releasing coat composition.

[0538] In a prophetic example of certain embodiments of osmotic dosage forms of the present invention, the manufacturing process for the control-releasing coat of the osmotic dosage form can hypothetically be as follows: Water is split into two portions of 15% and 85%. The anti-foaming agent and the emulsifying agent are then added to the 15% water portion, and mixed at 300 rpm to form portion A. In at least one embodiment, the anti-foaming agent is Simethicone C, and the emulsifying agent is Tween™ 80. A first lubricant is then added to the 85% water portion and mixed at 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 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 30 minutes at 500 rpm. In at least one embodiment, the aqueous dispersion of a neutral ester copolymer is Eudragit® NE30D. The resultant coat solution can then be used to coat the osmotic subcoated microparticles to a 35% weight gain with the following parameters: An inlet temperature of from 10°C to 60°C, preferably from 20°C to 40°C, and more preferably from 25°C to 35°C; an outlet temperature of from 10°C to 60°C, preferably from 20°C to 40°C, and more preferably from 25°C to 35°C; a product temperature of from 10°C to 60°C, preferably from 15°C to 35°C, and more preferably from 22°C to 27°C; an air flow of from 10 c.m/h to 180 c.m/h, preferably from 40 c.m/h to 120 c.m/h, and more preferably from 60 c.m/h to 80 c.m/h; and an atomizing pressure of from 0.5 bar to 4.5 bar, preferably from 1 bar to 3 bar, and more preferably 2 bar. The resultant coated microparticles can then be discharged from the coating chamber and overcured with the following parameters: A curing temperature of from 20°C to 65°C, preferably from 30°C to 55°C, and more preferably 40°C; and a curing time of from 2 hours to 120 hours, preferably from

10 hours to 40 hours, and more preferably 24 hours. Any other technology resulting in the coating formulation of the control-releasing coat of the osmotic dosage form that is consistent with the objects of the invention can also be used.

[0539] In at least one other embodiment, the osmotic dosage forms comprise a water-soluble or rapidly dissolving coat between the semipermeable membrane and the control-releasing 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 of the water-soluble coat are disclosed in U.S. Pat. Nos. 4,576,604 and 4,673,405, and the text Pharmaceutical Dosage Forms: Tablets Volume I, Second Edition. A. Lieberman. ed. 1989, Marcel Dekker, Inc. In certain embodiments, the rapidly dissolving coat can be soluble in saliva, gastric juices, or acidic fluids. Materials which are suitable for making the water soluble coat or layer can comprise, for example, water soluble polysaccharide gums such as carrageenan, fucoidan, gum ghatti, tragacanth, arabinogalactan, pectin, and xanthan; water-soluble salts of polysaccharide gums such as sodium alginate, sodium tragacanthin, and sodium gum ghattate; water-soluble hydroxyalkylcellulose wherein the alkyl member is straight or branched of 1 to 7 carbons such as, for example, hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose; synthetic water-soluble cellulose-based lamina formers such as, for example, methyl cellulose and its hydroxyalkyl methylcellulose cellulose derivatives such as a member chosen from the group of hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, and hydroxybutyl methylcellulose; croscarmellose sodium; other cellulose polymers such as sodium carboxymethylcellulose; and other materials known to those of ordinary skill in the art. 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(vinyl acetate) copolymer. The water soluble coating can comprise other pharmaceutical excipients that do or do not 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 of the 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 the bupropion salt from the osmotic dosage form so as to achieve the desired in-vitro release rates.

[0540] In embodiments where the core of the osmotic dosage form does not comprise an osmagent, the osmotic dosage forms can comprise an osmotic subcoat, which can surround the core of the osmotic dosage form. The osmotic subcoat comprises at least one osmotic agent and at least one hydrophilic polymer. The osmotic subcoat of this embodiment provides for the substantial separation of the bupropion salt from the osmotic agent into substantially separate compartments/layers. This separation can increase the stability of the bupropion salt by reducing possible unfavorable interactions between the bupropion salt and the osmagent, and/or between the bupropion salt and the components of the control-releasing coat. For example, the osmagent can be hygroscopic in nature, and can attract water that can lead to the degradation of the bupropion salt. Since the osmotic agent of these embodiments can be substantially separated from the bupropion salt, the bupropion salt can be less prone to degradation from the water drawn in by the osmagent. The control-releasing coat comprises a control-releasing polymer and optionally a plasticizer. The coated cores of the osmotic dosage form can be filled into capsules, or alternatively can be compressed into tablets using suitable excipients. In these embodiments the multiparticulate osmotic dosage form can utilize both diffusion and osmosis to control drug release, and can be incorporated into sustained release and/or delayed release dosage forms. In addition, in certain embodiments the osmotic pressure gradient and rate of release of the bupropion salt can be controlled by varying the level of the osmotic agent and/or the level of the hydrophilic polymer in the osmotic subcoat, without the need for a seal coat around the osmotic subcoat.

[0541] 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 salt. In at least one embodiment the release profile of the osmotic agent is substantially the same as the release profile of the bupropion salt. Such hydrophilic polymers useful in an osmotic subcoat of the present invention include by way of example, polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose, low

molecular weight hydroxypropyl methylcellulose (HPMC), polymethacrylate, ethyl cellulose, and mixtures thereof. In at least one embodiment, the hydrophilic polymer of the osmotic subcoat 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 subcoat. Examples of HPMC polymers that can be used in the osmotic subcoat include Pharmacoat® 606, Pharmacoat ® 606G, Pharmacoat ® 603, Methocel® E3, Methocel® E5, Methocel® E6, and mixtures thereof. The hydrophilic polymer of the osmotic subcoat can be present in an amount of from 1% to 30% by weight of the osmotic subcoat composition. For example, in certain embodiments the hydrophilic polymer is present in an amount of from 1% to 20%, in other embodiments from 3% to 10%, and in still other embodiments 7% by weight of the osmotic subcoat composition.

[0542] In at least one embodiment, the osmotic subcoat comprises 7% Pharmacoat® 606, 1% sodium chloride, and 92% water, by weight of the osmotic subcoat composition.

[0543] 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 60°C. The hydrophilic polymer is then added gradually to the solution. A magnetic stirrer can be used to aid in the mixing of the hydrophilic polymer to the solution of osmotic agent and water. The resultant osmotic subcoating solution can then be used to coat the core of the osmotic dosage form in a fluidized bed granulator, such as a granulator manufactured by Glatt (Germany) or Aeromatic (Switzerland) to the desired weight gain. An inlet temperature of from 10°C to 70°C, preferably from 30°C to 55°C, and more preferably from 40°C to 45°C; an outlet temperature of from 10°C to 70°C, preferably from 20°C to 45°C, and more preferably from 30°C to 35°C; a product temperature of from 10°C to 70°C, preferably from 20°C to 45°C, and more preferably from 30°C to 35°C; an air flow of from 10 c.m/h to 180 c.m/h; preferably from 40 c.m/h to 120 c.m/h; and more preferably from 60 c.m/h to 80 c.m/h; an atomizing pressure of from 0.5 bar to 4.5 bar, preferably from 1 bar to 3 bar, and more preferably 2 bar; a curing temperature of from 10°C to 70°C, preferably from 20°C to 50°C, and more preferably from 30°C to 40°C; and a curing time of from 5 minutes to 720 minutes; preferably from 10 minutes to 120 minutes, and more preferably 30 minutes. Any other technology

resulting in the coating formulation of the osmotic subcoat consistent with the objects of the invention can also be used.

[0544] The ratio of the components in the core, semipermeable membrane and/or water-soluble membrane and/or at least one control-releasing coat and/or osmotic subcoat as well as the amount of the various membranes or coats applied can be varied to control delivery of the bupropion salt either predominantly by diffusion across the surface of the semipermeable membrane to predominantly by osmotic pumping through the at least one passageway in the semipermeable membrane, and combinations thereof such that the dosage form can exhibit a modified-release, controlled-release, sustained-release, extended-release, prolonged-release, bi-phasic release, delayed-release profile or a combination of release profiles whereby the in-vitro release rates of the bupropion salt is such that after 2 hours from 0 to 20% by weight of the bupropion salt is released, after 4 hours from 15% to 45% by weight of the bupropion salt is released, after 8 hours, from 40% to 90% by weight of the bupropion salt is released, and after 16 hours, more than 80% by weight of the bupropion salt is released. In embodiments where the mode of exit of the bupropion salt comprises a plurality of pores, the amount of pore forming agent employed to achieve the desired in-vitro dissolution rates can be readily determined by those skilled in the drug delivery art.

[0545] In at least one embodiment, the core of the osmotic dosage form comprises bupropion hydrobromide. The proportion of the bupropion hydrobromide in the core can be from 40% to 99%, such as for example, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99% of the core dry weight.

[0546] 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 control-releasing coat, a water-soluble coat, an osmotic subcoat, or any combination thereof. The core of the osmotic dosage form has an effective osmotic pressure greater than that of the 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 of the osmotic dosage form. The at least one means for increasing the hydrostatic pressure inside the membrane or coat can be, for example, the bupropion 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 swellable. Examples of osmotically effective solutes are inorganic and organic salts and sugars. The bupropion salt can itself be an osmagent or can be combined with one or more 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-mannitol, urea, inositol, magnesium succinate, tartaric 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 amount of osmagent can range from , for example, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, or 95% of the core dry weight.

[0547] The osmagent useful in certain embodiments of the present invention can be any agent that can generate an osmotic pressure gradient for the transport of water from the external environment of use 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 of the present invention are soluble in aqueous and biological fluids, such as ionizing compounds, inherently polar compounds, inorganic acids, organic acids, 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 salt from the core of the osmotic dosage form. Examples of inorganic salts useful as osmagents include lithium chloride, lithium sulfate, lithium phosphate, magnesium chloride, magnesium 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 of salts of organic acids useful as osagents include sodium citrate, potassium acid tartrate, potassium bitartrate, sodium bitartrate, and mixtures thereof. Examples of ionizable solid acids useful as osmagents 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 of fructose glucose and mixtures thereof. In at least one embodiment the osmagent is selected from sodium chloride, sodium bromide, sodium bisulfate, potassium acid tartrate, ctric acid, mannitol, sucrose and mixtures thereof. Combinations of these osmagents is permissible. The osmagent can be present in an amount of from 0.1% to 50% of the dosage form weight. For example, in certain embodiments the osmagent is present in an amount of from 1% to 40%, and in other embodiments from 1% to 20% of the dosage form weight.

[0548] 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 polymers to be used as osmopolymers, when in contact with water and/or aqueous biological fluid, should not dissolve in water, hence maintaining their physical integrity. Such 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), poly(methylacrylate-co-styrene), poly(n-butyl methacrylate), poly(n-butyl-acrylate), poly(cyclododecyl acrylate), poly(benzyl acrylate), poly(butylacrylate), 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), 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., dextrans, water-soluble gums, starches, chemically modified starches), cellulose derivatives (e.g., cellulose esters, cellulose ethers, chemically modified cellulose, microcrystalline cellulose, sodium carboxymethylcellulose and methylcellulose), starches, Carbopol™, acidic carboxy polymer, Cyanamer™, polyacrylamides, cross-linked water-swellable indene-maleic anhydride polymers, Good-rite™, polyacrylic acid, polyethyleneoxide, starch graft copolymers, Aqua-Keeps™, acrylate polymer, diester cross-linked polyglucan, and any combination thereof.

[0549] In certain embodiments, the core of the osmotic dosage form further comprises a means for forcibly dispensing the bupropion salt from the core to the exterior of the dosage form. The at least one means for forcibly dispensing the bupropion salt can be any material which can swell in water and/or aqueous biological fluid and retain a significant fraction of water 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 thereof which 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 of the bupropion 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 means for forcibly dispensing the bupropion salt from the core of the 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 forcibly dispensing the bupropion 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, fumaric, tartaric, itaconic, maleic, citric, adipic, 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 between 1 to 200 parts of the at least one acid compound to the at least one basic compound or 1 to 200 parts of the at least one basic compound to the at least one acid compound. The means for generating gas is described, for example in US Pat. No. 4,235,236.

[0550] In at least one embodiment, the at least one means for forcibly dispensing the bupropion salt form the core of the osmotic dosage form comprises any material which can swell in water

and/or aqueous biological fluid and retain a significant fraction of water 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 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. Examples of hydrogels include poly(hydroxyalkyl methacrylates), poly(acrylamide), poly(methacrylamide), poly(N-vinyl-2-pyrrolidone), anionic and cationic hydrogels, polyelectrolyte complexes, a water-insoluble, water-swellable copolymer produced by forming a dispersion of finely divided copolymers of maleic anhydride with styrene, ethylene, propylene butylene or isobutylene cross-linked with from 0.001 to 0.5 moles of a polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer as disclosed in U.S. Pat. No. 3,989,586, the water-swellable polymers or N-vinyl lactams as disclosed in U.S. Pat. No. 3,992,652, semi-solid cross-linked poly(vinyl pyrrolidone), diester cross-linked polyglucan hydrogels as described in U.S. Pat. No. 4,002,173, the anionic hydrogels of heterocyclic N-vinyl monomers as disclosed in U.S. Pat. No. 4,036,788, the ionogenic hydrophilic gels as described in J. Biomedical Mater, Res., Vol. 7, pages 123 to 126, 1973, and the like. Some of the osmopolymers and hydrogels are interchangeable Such means can optionally be covered by a membrane or coat impermeable to the passage of the bupropion salt, 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.

[0551] In at least one other embodiment, the at least one means for forcibly dispensing the bupropion salt from the core of the osmotic dosage form comprises at least one osmotically effective solute surrounded by a membrane or coat impermeable to the passage of the bupropion 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, which asymmetric membrane can be permeable, semipermeable, perforated, or unperforated. The osmotically effective solutes include, for example, the osmagents described above.

[0552] In embodiments of the osmotic dosage form where the means for forcibly dispensing the bupropion salt is surrounded by a membrane or coat, at least one plasticizer 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 salt comprises a means for generating a gas, the membrane or coat should be stretchable so as to prevent rupturing of the membrane or coat during the period of delivery of the bupropion salt. US Patent No. 4,235,236 describes the manufacture of such a membrane or coat. Plasticizers, which can be used in these embodiments include, for example, cyclic and acyclic plasticizers, phthalates, phosphates, citrates, adipates, tartrates, sebacates, succinates, glycolates, glycerolates, benzoates, myristates, sulfonamides halogenated phenyls, poly(alkylene glycols), poly(alkylenediols), polyesters of alkylene glycols, dialkyl phthalates, dicycloalkyl phthalates, diaryl phthalates and mixed alkyl-aryl phthalates, such as for example, dimethyl phthalate, dipropyl phthalate, di(2-ethylhexyl)phthalate, di-isopropyl phthalate, diamyl phthalate and dicapryl phthalate; alkyl and aryl phosphates, such as for example, tributyl phosphate, trioctyl phosphate, tricresyl phosphate, trioctyl phosphate, 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; dialkyl 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 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 dipropionate and mixtures thereof. Other plasticizers include camphor, N-ethyl (o- and p-toulene) sulfonamide, chlorinated biphenyl, benzophenone, N-cyclohexyl-p-toluene sulfonamide, substituted epoxides and mixtures thereof.

[0553] The at least one means for forcibly dispensing the bupropion salt from the core of certain embodiments of the osmotic dosage form can be located such that it is approximately centrally located within the core of the osmotic dosage form and is surrounded by a layer comprising the bupropion salt. Such a configuration is disclosed in US Pat. No. 6,352,721. 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 acceptable excipient adjacent to a second layer comprising the means for forcibly dispensing the bupropion salt. Alternatively, the core of the osmotic dosage form comprises a multilayered structure in which the layer comprising the bupropion salt is sandwiched between two layers of the means for forcibly dispensing the bupropion salt from the osmotic dosage form.

Combinations

[0554] The present invention also contemplates combinations of the bupropion 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 present in an amount effective in the treatment of a condition. The present invention further provides a method for treating a condition, comprising administering to a patient an effective amount of a first component of bupropion 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 may be selected as the second drug include by way of example other depressants, anti-anxiety agents, steroidal and non-steroidal inflammatories, SSRIs, anti-migraine agents, anti-pain agents, anti-emetics, drugs for treating abuse such as nicotine, appetite modulators, anti-virals, vasodilators, anti-pain agents, et al. 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 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 hydrobromide include citalopram, escitalopram, venlafaxine, clozapine, melperone, amperozide, iloperidone, risperidone, quetiapene, olanzapine, ziprasidone, aripiprazole, reboxetine, Viagra®, sertraline, paroxetine, fluoxetine, gabapentin, valproic acid, amitriptyline, lofepramine, fluvoxamine, imipramine, mirtazapine, nefazodone, nortriptyline, SAM-E 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 hydrobromide and venlafaxine is provided.

[0555] In certain embodiments, combination products can be made by providing an overcoat to substantially surround the control-releasing coat of each microparticle. In certain embodiments, a pulsatile release of at least one other drug is achieved from the coated microparticles. This overcoat can be an immediate release overcoat that includes at least one other drug and at least one low viscosity hydrophilic polymer. The low-viscosity polymer provides for the immediate release of the other drug from the overcoat. In at least one embodiment, the low-visocity polymer used in the overcoat is hydroxypropyl methylcellulose (HPMC). The overcoat can also include a lubricant such as talc. As such, this embodiment 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 control-releasing coated microparticle in a second phase of drug release.

[0556] In addition, combinations of microparticles of the invention each with a different functional coating can be combined together in a dosage form. For example, by combining a first group of uncoated, 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, US2002/0098232, US2004/0197405, US 6,635,284, or US 6,228,398).

[0557] In other embodiments, the combination may comrise at least 2 different microparticles one of which contain bupropion hydrobromide and the other the second drug which are comprised in a capsule formulation.

[0558] While only specific combinations of the various features and components of the present invention have been discussed herein, it will be apparent to those of skill in the art that desired subsets of the disclosed features and components and/or alternative combinations of these features and components can be utilized as desired.

[0559] 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 of the control-releasing coat. It is possible to regulate the rate of hydration and permeability of the control-releasing coat so that the desired controlled-release profile can be achieved. There is no general preferred control-releasing coat thickness, as this will depend on the controlled release profile desired. Other parameters in combination with the thickness of the control-releasing coat include varying the concentrations of one or more of

the ingredients of the control-releasing coat composition, varying the curing temperature and length of time for curing the coated tablet microparticles, and in certain embodiments, varying the level of osmotic agent. The skilled artisan will know which parameters or combination of parameters to change for a desired controlled release profile.

4. STABILITY STUDIES

[0560] The enhanced stability of the bupropion hydrobromide, in particular compared to bupropion HCl, is clearly evident from degradation studies performed on the active pharmaceutical ingredient (API), alone, in the presence of excipients and in the form of XL tablets. The results are described in greater detail in the examples below.

[0561] The term "enhanced stability", "greater stability", "increased stability" or "more stable" as used herein means that the bupropion salt (bupropion hydrobromide), and compositions, formulations or medicaments comprising the bupropion salt, when exposed to like conditions, i.e., storage for at least 3, 4, 5 and/or at least 6 months under accelerated torage conditions, i.e., 40 degrees C at 75% relative humidity show less degradation as determined by the formation of at least one degradation product characteristic of bupropion degradation and/or the retention of potency, compared to otherwise similar compositions containing bupropion hydrochloride. This includes in particular compositions containing bupropion hydrobromide that show less degradation based on a reduced amount of at least one compound characteristic of bupropion degradation relative to an otherwise similar bupropion hydrochloride composition stored under similar accelerated storage conditions i.e., 40 degrees C at 75% humidity for at least 3 months, 4 months, 5 months and/or at least 6 months. Additionally another indicator of enhanced stability is that the bupropion HBr composition exhibits less fluctuation is an in vitro dissolution profile which shows less fluctuation relative to an otherwise similar bupropion HCl composition after prolonged storage under similar conditions and wherein disolution is assayed under similar conditions (media and time) particularly after being stored for at least 3 months, 4 months, 5 months and/or at least 6 months at 40 degrees C and 75% relative humidity.

[0562] By "less degradation" it is meant any measurable decrease in the amount of at least one impurity or degradation product characteristic of bupropion degradation or any measurable difference (enhancement or reduced fluctuation) in potency relative to an otherwise similar bupropion HCl composition after the compositions are stored for prolonged time, i.e., at least 3

months, 4 months, 5 months and/or at least 6 months at 40 degrees C at 75% relative humidity. . The "degradation products" include those listed on page 281 of the 26th edition of the USP and any other degradation products that may appear as peaks on a chromatogram during the assay. One indicator of enhanced potency is a bupropion HBr composition that exhibits less fluctuation in dissolution profile after prolonged storage, i.e at least 3, 4, 5 or 6 months at 40 degrees C and 75% relative humidity relative to an otherwise similar bupropion HCl composition assayed under similar dissolutionconditions.

[0563] A comparison of the stability of several bupropion salts, including the HBr, HCl, maleate, tosylate, fumarate, succinate, tartrate and citrate salts, was performed by placing these salts in both open and closed vials in a stability chamber kept at 40 degrees C and 75% relative humidity for various periods of time. The stability of the salts was evaluated based on the formation of the main degradation products (see below) as determined by HPLC analysis and the % potency (or assay) of the API, after specific time periods in the stability chamber. The effect of the addition of solvents, such as water, ethanol and isopropyl alcohol, was also studied.

[0564] The results unequivocally show that after at least 3 months or after at least 6 months the HBr salt of bupropion, on average, showed the least amount of degradation products and retained the highest activity of all of the salts tested. Accordingly the HBr salt possesses the greatest stability. These results are unexpected and would be in no way predictable by a person skilled in the art since none of the other salts that were tested showed this enhanced stability.

[0565] Further stability tests were performed by directly comparing bupropion HBr and bupropion HCl salts in forced degradation studies. These studies were performed in closed bottles in a stability chamber kept at 40 degrees C and 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 of impurities was consistently lower and the % potency was consistently higher for the HBr salt compared to the HCl salt.

[0566] Forced degradation studies were also performed on bupropion HBr and bupropion HCl API's in the presence of standard excipients used in pharmaceutical formulations. The amount of the main degradation products was observed at 24 and 48 hours after treatment at 55 oC, at 55 oC and 100% relative humidity and at 105 degrees C. Once again, it was unexpectedly found that the HBr salt showed the lowest amount of degradation (as determined by the formation of impurities) under these conditions.

[0567] The stability of the tablet formulations of bupropion HCl and HBr salts was also compared. With both salts, a tablet having the first control-releasing (EC) coat as well as a double coated tablet (with a control-releasing and moisture barrier coat) were evaluated. The tablets were placed individually on an open dish, and exposed to the accelerated conditions of 40 oC and 75% relative humidity in a stability chamber. After 13 and 20 days, the samples were assayed and impurity analysis was performed.

[0568] For the single coated bupropion HCl tablets, the main degradation impurities 3-CBZ and 852U77 were 0.12% and 0.38% respectively, whereas, for the bupropion HBr tablets, these values were 0.07% and 0.49% respectively. The other degradation impurities and the total unknowns were very similar for both products; however, the assay value for the HBr product was higher than the HCl. The difference in the assay and the impurity levels were more significant in the double coated tablets products. For the same period of the study the assay of the Bupropion HCl was lower (95.5% compared to 98.6 for bupropion HBr) and the level of the degradation and total unknowns were higher (3-CBZ: 0.28%, 852U77: 1.23%, 827U76: 0.10% and total 1.73%) than the Bupropion HBr (3-CBZ: 0.12%, 852U77: 0.41%, 827U76: 0.05% and total 0.75%).

[0569] The stability studies performed herein have clearly demonstrated the unexpected enhanced stability of buproprion HBr, in particular compared to bupropion HCl, which is used in all pharmaceutical forms currently available. This enhanced stability is seen with the API form alone, the API form plus excipients and the extended release and enhanced absorption tablets. Therefore pharmaceutical formulations comprising bupropion HBr are not only new, but also inventive due to their unexpected and beneficial enhanced stability properties. Pharmaceutical formulations comprising bupropion HBr will show enhanced shelf life and will withstand storage at higher temperatures and humidity levels compared with the currently used bupropion HCl formulations.

5. POLYMORPHIC FORMS

[0570] 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 of the products obtained in this study were determined by powder X-ray diffraction (PXRD). A RIGAKU miniflex instrument (Radiation Cu K∝, generator 30 KV, filter Ni) was used to obtain the PXRD data.

[0571] A standard procedure was established to generate bupropion hydrobromide, this standard procedure produces a first polymorphic form which has been termed polymorphic form I. The relative PXRD for form I is shown in Figure 54 and the differential scanning calorimetry (DSC) profile is shown in figure 55.

[0572] Bupropion HBr of form I has been used as the starting material in experiments to identify other polymorphic forms. Two additional polymorphic forms were identified and have been named form II and form III. Figures 56 and 57 show the PXRD data and DSC profile respectively of polymorphic form II. Figures 58 and 59 shown the PXRD data and DSC profile respectively of form III.

[0573] Polymorphic form II was obtained by recrystalization of form 1 from solvents or mixtures of solvents such as acetone-water, methanol, dichloromethane, toluene-methanol and dimethylcarbonate-methanol. Polymorphic form III was obtained by recrystalization of polymorphic form I in methanol. Table 80 provides a list of recrystalization conditions and the polymorphic form obtained under each set of conditions.

[0574] The three polymorphic forms were subjected to stability testing. Samples of the polymorphic forms were subjected to ICH conditions (40 °C, 75%R.H.) and PXRD data was obtained at 3 months and 6 months. All of the samples had the same PXRD profile indicating that this polymorphic form is stable at these conditions and is not changing or degrading. Samples of the polymorphic forms II and III were tested after 1 month under the same accelerated stability conditions. Polymorphic form II showed no change in the PXRD profile at that time while the PXRD profile of form III showed conversion to form II. This data suggests that polymorphic forms I and II are quite stable while polymorphic form III is not as stable as forms I and II under the test conditions.

[0575] Tables 99-104 contain exemplary 348 and 174 Bupropion HBr XL tablets according to the invention. Table 105 contains stability data for exemplary bupropion HBr formulations under accelerated conditions for different batches over diferent time periods.

[0576] As will be seen from the non-limiting examples described below, the coatings used in the present invention are quite versatile. For example, the length and time for the lagtime can be

controlled by the rate of hydration and the thickness of the modified release overcoat. Other parameters in combination with the thickness of the coatings include varying the concentrations of some of the ingredients of the coating compositions of the invention described and/or varying the curing temperature and length of curing the coated tablet cores. The skilled artisan will know which parameters or combination of parameters to change for a desired controlled release profile.

[0577] The following examples illustrate the present invention and are not intended to limit the scope of the present invention.

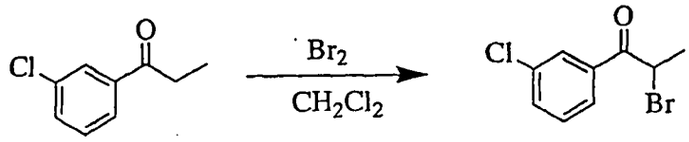
EXAMPLES

EXAMPLE 1: PREPARATION OF BUPROPRION HBR SALT

Buproprion HBr salt was prepared according to the method shown in Scheme 1:

Scheme 1

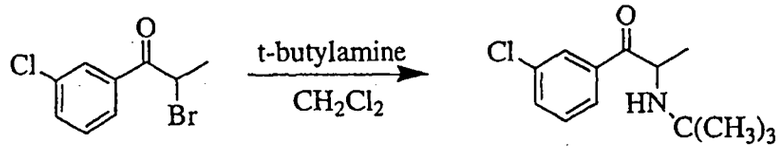
Bromination Reaction



3'-chloro-propiophenone
MW = 168.62

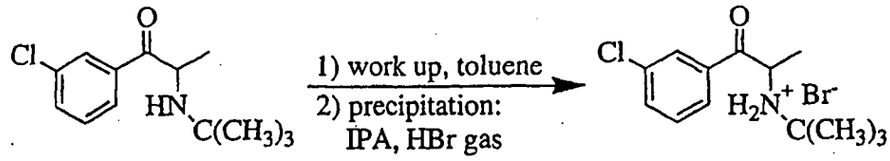
2-bromo-3'-chloro-propiophenone
MW = 247.52

Amination Reaction



2-t-butylamino-3'-chloro-propiophenone
MW = 239.75

Work Up / Precipitation / Drying



Bupropion.HBr
Intermediate

Finishing Step

Bupropion.HBr Intermediate —Sieving / Packaging→ Bupropion.HBr Final Release

(a) Bromination and condensation reactions

[0578] 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-butylamine. The second substitution reaction (the tert-butylamine amino-group 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 it was discharged in Kraft drums within double polyethylene bags.

[0579] In the last finishing step, the above intermediate was sieved to obtain the Final Release which was packed in Kraft drums within double polyethylene bags.

[0580] Elemental analysis of the bupropion HBr was carried out using a Fisons Elemental Analyser EA 1108. The results were consistent with the molecular formula of bupropion HBr.

EXAMPLE 2: PHYSIOCHEMICAL CHARACTERIZATION OF BURPOPION SALTS

[0581] The following bupropion salts were characterized against the HCl salt:

			Potency (HPLC) determined by R&D
Product ID	Lot#	Quantity	
Bupropion maleate	030/018	100 g	99.7 %
Bupropion tosylate	030/011/A	50 g	97.4 %
Bupropion Fumarate	031/1	10 g	89.8 %
Bupropion HBr	031/2	10 g	99.7 %
Bupropion succinate	031/3	10 g	97.6 %
Bupropion tartrate acid	031/5	10 g	84.9 %
Bupropion tartrate neutral	031/5B	10 g	51.7 %*
Bupropion citrate	031/8	10 g	85.0%

* uncorrected for potency

Thermal Analysis (DSC) Samples:

[0582] 2-5 mg of each salt was placed in an aluminium pan and covered with its lid. DSC was run for each sample at the rate of 10°C/min (for HBr salt, different rates were used to investigate for polymorphs) from 30°C to 400°C. TGA was also used for each of the HBr, HCl, maleate and tosylate salts.

Results and Discussion:

Physicochemical Data:

[0583] The eight salts were first evaluated by HPLC, KF, pH and DSC for purity, water content, aqueous pH and possible polymorphs. As shown in the Table 1, only the maleate, tosylate, HBr and succinate salts were sufficiently pure, the assay of others ranged between 51.7%% to 89.8%.

[0584] The salts were analysed by DSC (at 10oC/min from 30oC up to 400oC) and the pH (aq. 0.5%), and the moisture content by KF were also measured. The TGA was performed on the HCl, maleate, tosylate and HBr salts.

[0585] Maleate: DSC showed a melting endothermic peak at the onset temperature 199.1oC and a smaller sharp peak at 205oC. The moisture content was 0.10% and the pH of the aqueous solution of 0.5% was 4.29.

[0586] By re-crystallization in isopropyl alcohol (IPA)/EtOAc, the smaller peak almost disappeared. The TGA showed that this product was thermally stable to at least 150oC as 1.3% weight lost between room temperature and 100oC was observed. Like Bupropion HCl, no glass transition was observed when a heat-cool-heat experiment was done by TA instrument.

[0587] Fumarate: DSC showed multiple endothermic peaks at different onset temperatures (172.3, 182.3, 202 and 217oC). The moisture content was 0.09% and the pH of the aqueous solution of 0.5% was 3.84.

[0588] Tosylate: DSC showed a melting endothermic peak at the onset temperature 150oC, a smaller peak at 90oC and multiple peaks at higher temperature (> 200oC, probably decomposition). The peak at 90oC was probably due to the solvent isopropyl acetate. The moisture content was 1.71% and the pH of the aqueous solution of 0.5% was 5.56.

[0589] By re-crystallization in acetonitrile/hexane or acetonitrile/EtOAc, the small peak at 90oC disappeared, the moisture content dropped to 0.23%, and the pH changed to 5.88. After two months, the re-crystallized sample was retested for moisture content and found to be 0.18%. Therefore, there was a difference between the original and the re-crystallized salt in terms of purity and moisture content (originally thought to be hydrated and/or hygroscopic).

[0590] The TGA showed that this product was not thermally stable as 1.3% weight lost was observed between room temperature and 100oC. Also the sample gave a residue of 10.3% at 400oC as compared to minimal residues for bupropion HCl and maleate. The Heat-Cool-Heat experiment was done by TA instrument showed a glass transition (Tg) at 45C. The Tg indicates that the morphology is amorphous rather than crystalline.

[0591] HBr: DSC showed melting endothermic peak at temperature 224oC, with a shoulder peak. The sample was run at different temperature rates, 1, 10, 15 & 20oC/min to seek for possible polymorphs. No significant differences were observed for the endothermic peak shape at different temperature rates. By-crystallization of the HBr salt in different solvents or by internal synthesis starting from 3-chloropropiophenone, no improvements in the shape of the endothermic peak melting at ~ 224oC was observed (i.e, still the same shoulder at 10oC or higher rates). A Heat-Cool-Heat experiment was done by TA instrument showed a glass transition (Tg) at 23oC.

[0592] The moisture content was 0.00% and the pH of the aqueous solution of 0.5% was 5.92.

[0593] Other salts: The DSC results of other salts show multiple melting endothermic peaks . The pH, and the water content of all of the salts are shown in Table 2.

[0594] A comparison of the solubility & other physical properties of bupropion HBr vs bupropion HCl is presented in Table 3.

[0595] Hygroscopicity of Bupropion HBr:

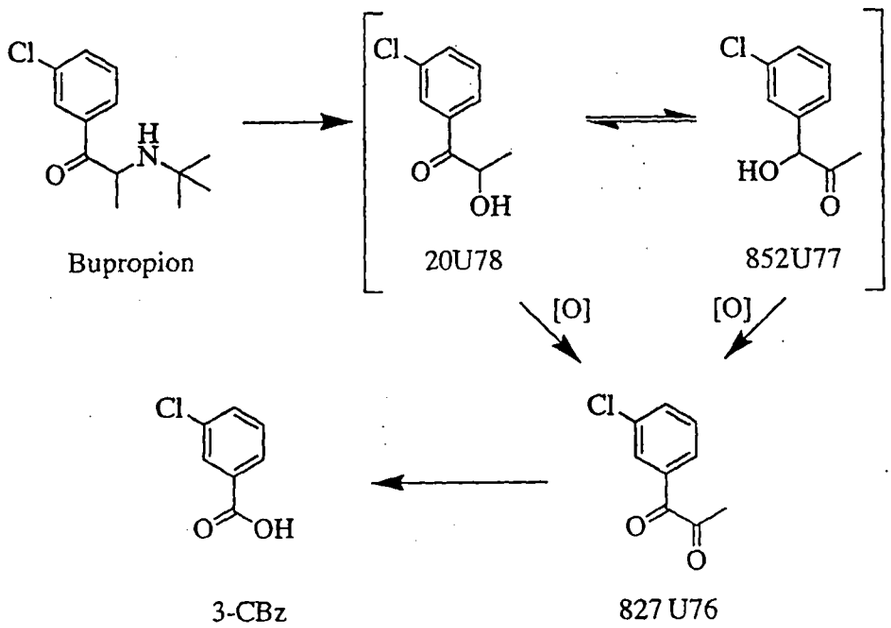
[0596] The Dynamic Vapour Sorption (DVS) analysis of bupropion HBr suggests that the sample is a crystalline anhydrate and has very little water uptake capacity (i.e. non-hygroscopic). The sample of bupropion HBr shows no significant water uptake over the range 0%RH-90%RH. The maximum water uptake was measured at 0.14%weight at 90%RH. A DVS profile for bupropion HBr is shown in Figure 1 and DVS isotherm data for bupropion HBr is shown in Figure 2.

EXAMPLE 3: FORCED DEGRADATION STABILITY STUDY

[0597] The samples of each salt and the spiked salts with the bupropion HCl XL were prepared under the conditions mentioned in Table 4. The samples were placed in the stability chamber at 40°C/75%RH, pulled out at 10, 20 and 32 days and analysed by HPLC for assay and impurities. The stability of the bupropion salts were evaluated based on the formation of the main degradation product 3-chlorobenzoic acid (3-CBZ) and the intermediate degradation products

diketone 827U76 and the ketohydroxyl derivatives (20U78 and 852U77) (Scheme 2). The 3-chlorobenzoic acid is formed as a result of the oxidation/hydrolysis of the parent compound bupropion salts.

Scheme 2



[0598] As mentioned above, the stability samples were prepared in 2mL vials and used directly for assay and impurity analysis by HPLC without further sample preparations to minimize errors.

[0599] The 10 days forced degradation studies on these salts showed that the succinate, tartrate and citrate (with or without mixing with excipients in closed vials) were not stable under the conditions mentioned in Table 4. The assay substantially dropped down, the level of known and unknown impurities increased and the colours of these salts changed from the original white powders to yellow semi liquid products. Therefore, further study on these salts was not continued.

[0600] The 10, 20 and 32 days stability time points for the maleate, tosylate, HBr, and fumarate salts were continued in parallel to Bupropion HCl. The results are shown in Figures 3-10. The assay and impurity results for 20-days in closed vials for these five salts were compared for salt plus excipients and are presented Figures 3 and 4. Figures 5-7 show the results for the drug salts

(DS) kept for 32 days in closed vials and spiked with water, water-isopropyl alcohol (IPA)-ethanol (EtOH) and IPA-EtOH.

[0601] In the closed vial assays, it is of note that the impurities (3-CBZ, 852U77 & total) in the HBr salt were the lowest compared to all of the other salts including HCl (see Figure 3). The levels of 852U77 in the other salts were comparable with HCl, however, the levels of 3-CBZ and, in particular levels of the total impurities were more with the other salts than HCl. In the assay results (%potency), the tosylate and the HCl salts had similar potency after the 20 days in a closed vial (Figure 4). In the assay study, the order of stability for the bupropion salts was as follows: HBr>HCl≈tosylate>fumarate>maleate).

[0602] The stability of the salts was then evaluated under more aggressive conditions. The drug salts (DS) and excipients were spiked with water, water plus EtOH and IPA and EtOH and IPA. As can be seen from the results shown in Figures 5-7, the order of stability (assay) of the salts can be summarised as follows:

Stability with water:	tosylate>maleate>HCl>HBr>fumarate.
Stability with IPA & EtOH:	HCl> HBr> tosylate> maleate>fumarate

[0603] Tosylate and maleate salts were more stable than other salts when exposed directly to water, and less stable when exposed to the organic solvents IPA & EtOH.

[0604] The HCl and HBr salts were more stable than other salts when exposed directly to IPA & EtOH and less stable with water. The fumarate salt was neither stable in water nor in the organic solvents IPA & EtOH.

[0605] The level of the impurities (known, unknown & total) varied in each of the salts under the conditions of this experiment. The content of each of the major impurities (3CBZ & 52U77) and the total impurities was as follows (Figures 8-10):

In water,	3-CBZ:	HCl> HBr≈maleate=fumarate
	852U77:	fumarate>HBr>maleate>HCl
	Total imp.	fumarate>HBr>HCl>tosylate>maleate
In IPA/EtOH:	3-CBZ:	maleate> HBr> HCl> Fumarate
	852U77:	fumarate>HBr ≈ HCl ≈maleate≈tosylate
	Total imp.	fumarate>maleate>HBr>HCl>tosylate

[0606] Based on the forced degradation stability studies conducted on the above bupropion salts, the stability of oxalate, citrate, succinate and tartarate were shown to be very poor for the DS and

the spiked DS (20 days: discoloration, Low assay & high level of degradation impurities). The HBr, tosylate, maleate and to some extent fumarate salts are good candidates for further studies. Among the latter salts, HBr was the best candidate due to its superior stability in a closed container, lowest water content, non-hygroscopic and its easy preparation.

[0607] The tosylate salt also showed good stability, although it was not as pure as the HBr, HCl or maleate. The tosylate salt, however, does not have an acceptable toxicity profile.

[0608] It also was found that the presence of the organic solvents ethanol and isopropyl alcohol have significant impact on the stability of these salts.

EXAMPLE 4: COMPARATIVE FORCED DEGRADATION STUDIES OF BUPROPION HCl AND BUPROPION HBr API SALTS

[0609] The stability of bupropion HCl and bupropion HBr API salts were further evaluated under the accelerated conditions of 40oC/75%RH in a stability chamber. The samples were exposed to the above conditions in a closed bottle for few days, and then subjected to HPLC analysis. The amount of the main degradation products present after treatment were compared with those amounts that were present initially.

[0610] Accurately quantities of each API were weighed individually in 50-mL amber glass bottles as shown in the Table 5. The bottles were closed and placed in the stability chamber at 40oC/75%RH. The samples were analysed after 14 and 24 days (study-1) and 10 days (study II), in a quantitative manner by direct treatment of the whole content of the bottle as per the HPLC standard test method (P05.901.10).

[0611] As shown in the Table 6, the resulting degradation products in both bupropion HCl and bupropion HBr were either similar or better for the HBr salt.

[0612] The above study was repeated on two batches of each of the APIs for 10 days. As shown in table 7, the level of impurities in the case of bupropion HBr salt was lower than bupropion HCl, also the assay value for the latter was lower than that for the HBr salt.

[0613] EXAMPLE 5: BUPROPION HBr EXTENDED RELEASE (XL) TABLETS

[0614] The aim of this example was to describe the development of bupropion HBr XL (174 and 348mg). Granulation, tabletting and coating procedures are all described thoroughly in this example. In vitro testing was conducted on the cores, the EC coated cores and the final coated tablets in order to determine which formulation gave the desired results.

[0615] From their structural formulae, it is observable that the difference between bupropion HCl 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 dissolution studies.

[0616] It was previously observed that when 150mg 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, which was the target. Studies showed that 174mg of bupropion HBr gave a base value release of 130mg and is therefore why 174mg was used as opposed to 150mg bupropion HBr.

[0617] Bupropion HBr XL – Granulation Process

[0618] A summary of the manufacturing process used for the preparation of bupropion HBr XL tablets is shown in Figure 11.

[0619] The following materials were used in the granulation of the immediate release core of the bupropion HBr EA tablets: bupropion HBr, polyvinyl alcohol (PVA) and purified water. Once granulated, lubricant (Compritol 888) was added to complete the formulation.

[0620] Each Trial was divided into 5 parts. The percentage of API in each formulation was 93.75%; the percentage of PVA in each formulation was 3.125%. A summary of the breakdown of each trial per part is described in Table 8.

[0621] The PVA was dissolved into the purified water using a magnetic stirrer and a clear colourless solution was made.

[0622] The NIRO Fluid Bed was used to granulate the bupropion HBr Granules with the PVA solution in a process known as wet massing. Figure 12 shows a summary of the granulation procedure.

[0623] The Bupropion HBr was loaded into the fluid bed and granulation was initiated. The specifications that were used as guidelines are listed in Table 9.

[0624] Loss on Drying was determined after each granulation using the Moisture Analyzer. A 1g sample was taken and loaded into the moisture analyzer. The sample ran for 5 minutes at a temperature of 105°C.

[0625] Upon completion of each batch part's granulation, the five parts were combined together. They were hand screened using Mesh No. 14 (1.4mm) and any oversized granulation was passed through the Comil fitted with a 2mm screen.

[0626] Compritol 888 was used as a lubricant in the formulation. The screened bupropion HBr granules and the Compritol 888 were loaded into the V-blender and were blended for 5 minutes. The Compritol 888 made up 3.125% of the formulation. The final granule batch size is described in Table 10.

Bupropion HBr XL – Tabletting Process

[0627] The Beta Press was used to compress the Bupropion HBr 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 tablets. Tooling was polished prior to each run.

[0628] 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 in order to compensate for the fact that bupropion HBr was being used in place of bupropion HCl. The individual tablet weights had a control limit of ±5%, and the average tablet weight had a control limit of ±3% (using ten tablets).

[0629] 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 hardness, which was 6.0-12.0 SC for both the 174mg and 348mg tablets.

[0630] Friability was determined using tablets that equaled a weight of 6.5g in a friability tester for 4 minutes at 25 rpm. Tablets were de-dusted before and after testing. A weight loss of less than 0.8% was used as the criteria in order to accept or reject a batch.

[0631] Table 11 summarizes the specifications of the tablet press set-up. All the specifications were kept within the range and at the setting that was assigned, throughout all of the batches.

[0632] Table 12 summarizes the specifications that were kept constant throughout the compression of all the batches.

[0633] The flow chart shown in Figure 12 describes the steps that led up to and including the tabletting process. Figure 13 shows a summary of the tabletting procedure.

Bupropion HBr XL – Coating Process

[0634] A summary of the coating process used for the coating of the Bupropion HBr XL tablets is shown in Figure 14. The first coat is an Ethocel coat that controls the release, which is followed by a final coat that acts as a moisture barrier.

[0635] For the Ethocel coating and final coating of the Bupropion HBr XL tablets, the 15 inches O'Hara Labcoat II System was used. An attached spraying nozzle and a propeller mixer were also used.

[0636] Several Ethocel coating solutions were developed and used to coat the Bupropion HBr tablets. The Ethocel coating layer was placed on the tablets containing one of the formulations listed in Table 13.

[0637] In formulation 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, Ethocel 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).

[0638] In formulation 2, PEG4000 was placed into a beaker with the Dibutyl Sebacate and was 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, Ethocel was added and stirred for 30 minutes. Following that, Povidone was added and allowed to stir for an overnight period (15-20 hours).

[0639] In formulation 3, Ethyl Alcohol 95% was placed in a stainless steel container. While stirring, PEG 4000 was added and allowed to dissolve. Once dissolved, Ethocel 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).

[0640] Two Final coating solutions were developed and used to coat the Bupropion HBr tablets after they had been first coated with the Ethocel coat.

[0641] One of the following formulations shown in Table 14 was used to coat the tablets with a final coat.

[0642] In Formulation A, the purified water was placed in a glass beaker and Chroma-Tone DEB 5156-CLE was added and allowed to mix for 15 minutes. The Eudragit was passed through a Mesh screen (no. 60) prior to use. Following this, the Eudragit was added to the beaker and was stirred for 15 more minutes.

[0643] In Formulation B, part 1 of the 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 Eudragit Suspension and left to stir for 45 minutes. The Eudragit was passed through a Mesh screen (no. 60) prior to use. In a separate beaker, part 2 of the purified water was added to the Syloid 244FP and mixed until it was completely dissolved (10 minutes). Finally the Syloid Suspension was added to the Eudragit Suspension and left to stir for another 10 minutes.

[0644] Table 15 summarizes the specifications that were monitored in the Ethocel coating process and their ranges.

[0645] Table 16 summarizes the specifications that were monitored in the final coating process and their ranges.

[0646] In-vitro Studies on the Bupropion HBr cores

[0647] Dissolution was performed on the Bupropion HBr cores, on the different weight gains of Ethocel coated cores and on the different weight gains of final coated tablets. USP-1 method was used to conduct these studies. The dissolution test was performed using 900mL of 0.1N HCl and at a speed of 75rpm. Samples were taken at every hour for 16 hours. The dissolution profiles were obtained by plotting the cumulative percent of API dissolved against sampling time points. Sink conditions were maintained throughout all the experiments.

[0648] 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 (SGF) 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 by12 hours in 900mL of Phosphate Buffer Simulated Intestinal Fluid (SIF) at a pH of 6.8. These results were plotted with the in-vivo data and the Bupropion HCl data in order for a comparison to be made.

Study on Batch BUP-HBr-XL-009-5

[0649] The formulation was granulated using NIRO Fluid Bed. After granulation was completed, the batch was screened and then prior to compression the lubricant (Compritol 888) was added. The final blend was compressed into 348mg tablets using the Beta press with 9mm and 10mm standard, round, concave tooling. Table 17 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 any, on the dissolution (Figure 15). Dissolution was conducted on the 348mg cores in order to determine their release (Figure 16).

[0650] The granulation results show that the average granulation time is 2.0 hours and the average LOD % is 0.345%. Tables 18 and 19 summarize the theoretical and actual values of the parameters that were monitored in the compression process using the 9mm and 10mm tooling, respectively.

[0651] 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.

[0652] Tablets with a hardness of 4kp, 6-7kp and 9-10kp were compressed and the dissolution profiles of each were shown in Figure 15. It was observed that there was no significant difference between the three different hardness ranges.

[0653] The dissolution profiles of the 348mg (Figure 16) and 174mg cores (Figure 17) showed that the cores were releasing approximately 100 percent of API in an hour.

[0654] Dissolution of the 10mm, 348mg cores was done also in order to see if these tablets released faster when compared to the 9mm cores due to their larger surface area (Figure 17).

[0655] When the dissolution results of the 9mm and 10mm cores were compared (Figure 18), 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 BUP-HBr-XL-021-5

[0656] The Formulation was granulated using NIRO Fluid Bed. The final blend was compressed into 174mg tablets using the Beta press with 7mm standard, round, concave, stainless steel tooling. Table 20 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 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 19).

[0657] The granulation results show that the granulation time is 2 hours 6 minutes and the average LOD % is 0.26%. Table 21 summarizes the theoretical and actual values of the parameters that were monitored in the compression process using the 7mm tooling.

[0658] The dissolution profile of the 174mg (Figure 19) showed that the cores were releasing approximately 100 percent of API in an hour.

Study on Batch BUP-HBr-XL-348mg-013-5

[0659] Using 348mg tablets, an Ethocel coating followed by a Final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0660] The materials used in the Ethocel (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 22.

[0661] 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.

[0662] 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 23 at 28mg, 30mg, 32mg, and 34mg weight gains.

[0663] The dissolution profile (Figure 20) shows that the tablets with the 34mg weight gain of EC coating released Bupropion HBr the slowest when compared to the others and that the tablets with the 28mg weight gain released Bupropion HBr the fastest when compared to the other weight gains.

[0664] The materials used in the final coating, their percent contribution to the total solution, the amounts of each in the batch, the amount of solid contribution in grams and the percentage of the solids in the solution were all listed in Table 24.

[0665] 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.

[0666] After this trial run, Chroma-Tone was no longer used due to the formulation problems it caused. First, it limited the composition of the formulation due to its inflexibility, as Syloid, 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. Chroma-Tone can, however, still be considered an option for the formulation but different grades and mixtures would need to be used and made in order to accommodate the Bupropion HBr XL tablets.

[0667] It took 31 minutes to add a 7mg weight gain of the final coating solution to the tablets.

[0668] Tablet weights were taken and recorded in Table 25 at 4mg, 5mg, 6mg and 7mg weight gains.

[0669] The dissolution profile (Figure 21) shows that the tablets with the 7mg weight gain of Final coating released the slowest when compared to the other two weight gains (5mg and 6mg weight gains).

Study on Batch BUP-HBr-XL-348mg-018-5

[0670] Using 348mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0671] The materials used in the Ethocel (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 26.

[0672] 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.

[0673] The coating process of this trial took 2 hours and 13 minutes to obtain a 32mg weight gain. Tablet weights were taken and recorded in Table 27 at 26mg, 28mg, 30mg, and 32mg weight gains.

[0674] Figure 22 shows that the tablets with the 30mg and 32 mg weight gain of EC coating solution released at almost the same rate. The tablets with the 32mg weight gain 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 of both weight gains was similar (91.32%).

[0675] The materials used in the final coating, their percent contribution to the total solution, the amounts of each in the batch, the amount of solid contribution in grams and the percentage of the solids in the solution were all listed in Table 28.

[0676] 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.

[0677] It took 41 minutes to add a 7mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded in Table 29 at 4mg, 5mg, 6mg, and 7mg weight gains.

[0678] Figure 23 shows the release profile of the tablets with the 7mg weight gain of Final coating.

Study on Batch BUP-HBr-XL-174mg-022-5

[0679] Using 174mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0680] The materials used in the Ethocel (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 30.

[0681] 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.

[0682] It took 4 hours and 30 minutes to add a 30mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 20mg, 22mg, 24mg, 26mg, 28mg, 29mg, and 30mg weight gains and were recorded in Table 31.

[0683] Figure 24 shows the % dissolved of each of the samples with different weight gains of EC coating (22mg, 24mg, 28mg and 30 mg weight gains). From the graph, it was evident that the tablets with the 30mg weight gain of EC coating released slower than the other weight gains. When the release rates of the tablets with the 30mg and the 28mg weight gains were compared, there was only a slight difference noticed in the release. The f2 similarity factor confirmed the similarity of the two releases (92.34%).

[0684] The materials used in the final coating, their percent contribution to the total solution, the amounts of each in the batch, the amount of solid contribution in grams and the percentage of the solids in the solution were all listed in Table 32.

[0685] 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.

[0686] It took 1 hour and 26 minutes to add a 7mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded in Table 33 at 4mg, 5mg, 6mg, and 7mg weight gains.

[0687] The dissolution profile (Figure 25) shows that the tablets with the 7mg weight gain of final coating released the slowest, in comparison to the 5mg and the 6 mg weight gains.

Study on Batch BUP-HBr-XL-348mg-023-5

[0688] Using 348mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0689] The materials used in the Ethocel (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 34.

[0690] 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.

[0691] It took 2 hours and 16 minutes to add a 32mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 26mg, 28mg, 30mg, and 32mg weight gains and were recorded in Table 35.

[0692] The dissolution profile (Figure 26) shows that the tablets with the 32mg weight gain of EC coating, when compared to the tablets with the 26mg, 28mg and the 30mg weight gain of EC coating, released at the slowest rate.

Study on Batch BUP-HBr-XL-348mg-025-5

[0693] Using 348mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0694] The materials used in the Ethocel (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 36.

[0695] 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.

[0696] It took 2 hours and 13 minutes to add a 32mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 26mg, 28mg, 30mg, and 32mg weight gains and were recorded in Table 37.

[0697] The dissolution profile (Figure 27) shows that the tablets with the 32mg weight gain of EC 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 EC coating to those with 30mg weight gain of EC coating, the tablets with the 32mg weight gain released slower up until 10 hours. The f2 similarity factor showed that the release of the tablets with the 30mg and 32mg weight gains were in fact similar (93.72%).

[0698] The materials used in the final coating, their percent contribution to the total solution, the amounts of each in the batch, the amount of solid contribution in grams and the percentage of the solids in the solution were all listed in Table 38.

[0699] 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.

[0700] The coating solution was altered for this batch by changing the percentage of solid from each of the solid components in the solution. The percentage of Eudragit solid contribution was decreased from 65% to 56.5%. The percentage of Syloid, Carbowax and Triethyl Citrate were increased from 25%, 6.65% and 3.39% to 30%, 9% and 4.5%, respectively.

[0701] It took 40 minutes to add a 7mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded (Table 39) at 4mg, 5mg, 6mg, and 7mg weight gains.

[0702] The dissolution profile (Figure 28) 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 the 6mg weight gain released similarly to those with the 7mg weight gain of Final coating (93.33%).

Study on Batch BUP-HBr-XL-348mg-026-5

[0703] Using 348mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0704] The materials used in the Ethocel (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 40.

[0705] 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.

[0706] It took 2 hours and 11 minutes to add a 32mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 26mg, 28mg, 30mg, and 32mg weight gains and were recorded in Table 41.

[0707] The dissolution profile (Figure 29) shows that the tablets with the 32mg weight gain of EC coating released the slowest when compared to the other three samples with lower weight gains of EC coating (26mg, 28mg and 30mg).

[0708] Study on Batch BUP-HBr-XL-174mg-027-5

[0709] Using 174mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0710] The materials used in the Ethocel (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 42.

[0711] 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.

[0712] It took 3 hours and 29 minutes to add a 32mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 22mg, 24mg, and 26mg weight gains and were recorded in Table 43.

[0713] The dissolution profile (Figure 30) shows that the tablets with the 26mg weight gain of EC coating released the slowest of the three samples tested.

[0714] The materials used in the final coating, their percent contribution to the total solution, the amounts in each in the batch, the amount of solid contribution in grams and the percentage of the solids in the solution were all listed in Table 44.

[0715] 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.

[0716] It took 1 hour and 17 minutes to add a 7mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded in Table 45 at 4mg, 5mg, 6mg, and 7mg weight gains.

[0717] The dissolution profile (Figure 31) shows that the tablets with the 7mg weight gain of final 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.

EXAMPLE 6: BUPROPRPION HBr ENHANCED ABSORPTION (EA) TABLETS

[0718] This example describes the development of bupropion EA "Enhanced Absorption" tablets (150mg and 300mg). Granulation, tabletting and coating procedures are all described thoroughly in this example. In vitro testing was conducted on the EC coated cores in order to determine which formulation gave the desired results.

[0719] Bupropion HBr was used in this study and its only difference to Bupropion HCl is the salt. A major advantage of an enhanced absorption composition can be lessening the amount of drug in the composition, which in turn can lead to a reduction of side effects.

[0720] The overall process for the development of bupropion HBr EA tablets is shown in Figure 32.

Bupropion HBr EA – Granulation Process

[0721] A summary of the granulation process of the bupropion HBr EA tablets is shown in Figure 33.

[0722] The following materials were used in the granulation of the immediate release core of the bupropion HBr EA tablets: bupropion HBr, polyvinyl alcohol and purified water. Once granulated, lubricant (Compritol 888) was added to complete the formulation. It must be noted that the granulation procedure for the bupropion HBr XL and Bupropion HBr EA are the same.

[0723] Each trial was divided into 5 parts. The percentage of API in each formulation was 93.75% and the percentage of PVA in each formulation was 3.125%. A summary of the breakdown of each trial per part was described in Table 46.

[0724] The Polyvinyl Alcohol was dissolved into the purified water using a magnetic stirrer and a clear colourless solution was made.

[0725] The NIRO Fluid Bed was used to granulate the Bupropion HBr Granules with the PVA solution in a process known as wet massing.

[0726] The Bupropion HBr was loaded into the fluid bed and granulation was initiated. The specifications that were used as guidelines were listed in Table 47.

[0727] Loss on Drying was determined after each granulation using the Moisture Analyzer. A 1g sample was taken and loaded into the moisture analyzer. The sample ran for 5 minutes at a temperature of 105°C.

[0728] Upon completion of each batch part's granulation, the five parts were combined together. They were hand screened using Mesh No. 14 (1.4mm) and any oversized granulation was passed through the Comil fitted with a 2mm screen.

[0729] Compritol 888 was used as a lubricant in the formulation. The screened Bupropion HBr granules and the Compritol 888 were loaded into the V-blender and were blended for 5 minutes. The Compritol 888 made up 3.125% of the formulation. The final granule batch size was described in Table 48.

Bupropion HBr EA – Tabletting Process

[0730] The Beta Press was used to compress the Bupropion HBr tablets. Depending on the dose of the tablet, 150mg or 300mg, different tooling sets were used. The 7mm punches were used to compress the 150mg tablets and 9mm punches were used to compress the 300mg tablets. Tooling was polished prior to each run.

[0731] The tablet weights were determined as being 160.0mg for the 150mg dose tablets and 320.0mg for the 300mg dose tablets. These adjustments to tablet weight were made in order to compensate for the fact that bupropion HBr was being used in place of bupropion HCl. Prior investigations showed that bupropion HBr tablets with the above stated weights gave in vitro results similar to those of the 150mg and 300mg bupropion HCl tablets. The individual tablet weights had a control limit of ±5%, and the average tablet weight had a control limit of ±3% (using ten tablets).

[0732] 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 hardness, which was 6.0-12.0 SC for both the 174mg and 348mg tablets.

[0733] Friability was determined using tablets that equaled a weight of 6.5g in a friability tester for 4 minutes at 25 rpm. Tablets were de-dusted before and after testing. A weight loss of less than 0.8% was used as the criteria in order to accept or reject a batch.

[0734] Table 49 summarizes the specifications of the tablet press set-up. All the specifications were kept within the range and at the setting that was assigned, throughout all of the batches.

[0735] Table 50 summarizes the specifications that were kept constant throughout the compression of all the batches.

Bupropion HBr EA – Coating Process

[0736] A summary of the coating process of the 150 mg and 300 mg bupropion HBr EA tablets with an Ethocel Coating is shown in Figure 35.

[0737] For the Ethocel coating of the Bupropion HBr EA tablets, the 15 inches O'Hara Labcoat II System was used. An attached spraying nozzle and a propeller mixer were also used.

[0738] Several Ethocel coating solutions were developed and used to coat the Bupropion HBr tablets. An Ethocel coating layer was placed on the tablets containing one of the formulations listed in Table 51.

[0739] In formulation 1, Ethyl Alcohol 200 proof was weighed out in a stainless steel container. While stirring, PEG 4000 was added and allowed to dissolve. Once dissolved, Ethocel 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).

[0740] In formulation 2, PEG4000 was placed into a beaker with the Dibutyl Sebacate and was stirred until it dissolved. This was added to the Ethyl Alcohol 200 proof that had already been

weighed out in a stainless steel container. Following this, Ethocel was added and stirred for 30 minutes. Thereafter, Povidone was added and allowed to stir for an overnight period (15-20 hours).

[0741] In formulation 3, Ethyl Alcohol 200 proof was placed in a stainless steel container. While stirring, Dibutyl Sebacate was added and allowed to dissolve. Once dissolved, Ethocel 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).

[0742] In formulation 4, Ethyl Alcohol 95% USP was weighed out in a stainless steel container. While stirring, PEG 4000 was added and allowed to dissolve. Once dissolved, Ethocel 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).

[0743] Table 52 summarizes the specifications that were monitored in the coating process and their ranges.

In-vitro Studies on the Bupropion HBr cores

[0744] Dissolution was performed on the Bupropion HBr cores and on the different weight gains of Ethocel coated cores. USP-1 method was used to conduct these studies. The dissolution test was performed using 900mL of 0.1N HCl and at a speed of 75rpm. Samples were taken at every hour for 16 hours. The dissolution profiles were obtained by plotting the cumulative percent of API dissolved against sampling time points. Sink conditions were maintained throughout all the experiments.

[0745] 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 (SGF) 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 by12 hours in 900mL of Phosphate Buffer Simulated Intestinal Fluid (SIF) at a pH of 6.8. These results were plotted with the in-vitro data and the Bupropion HCl data in order for a comparison to be made.

Study on Batch BUP-HBr-XL-016-5

[0746] The formulation was granulated using NIRO Fluid Bed. The final blend was compressed into 300mg tablets using the Beta press with 9mm round, concave tooling and into 150mg tablets with 7mm round, concave tooling. Table 53 describes the amounts of each material in the granulation of the 300mg tablets and Table 54 describes the amounts for the 150mg tablets. It

was noted that they were the same; the only variation was the tablet weight, which was adjusted at the compression stage. A first compression run was done to produce tablets with different hardness values so as to determine the effects of hardness, if any, on the dissolution (Figure 36). Dissolution was conducted on the 300mg and 150mg cores in order to determine their release (Figures 37and 38, respectively). After granulation was completed, the batch was screened and then prior to compression, the lubricant (Compritol 888) was added.

[0747] The granulation results show that the average granulation time is 2.0 hours and the average LOD % is 0.342%. Table 55 and Table 56 summarize the theoretical and actual values of the parameters that were monitored in the compression process using the 9mm and 7mm tooling respectively.

[0748] Figure 36 shows that the different hardness ranges did not rastically affect the dissolution profiles. The dissolution profiles of the 300mg (Figure 37) and 150mg cores (Figure 38) show that the cores were releasing approximately 100 percent of API in an hour.

Study on Batch BUP-HBr-EA-300mg-001-5

[0749] Using 300mg Bupropion HBr core tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0750] The materials used in the Ethocel (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 57.

[0751] The parameters are as follows: Spray Rate: 14 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C ± 2°C; and Supply Air Flow: 200 CFW.

[0752] It took 4 hours and 4 minutes to coat the tablets with a weight gain of 54mg. Tablet weights were taken and recorded in Table 58 at 44mg, 46mg, 48mg, 50mg 52mg, and 54mg weight gains.

[0753] The dissolution profile (Figure 39) shows that the tablets with the 44mg weight gain released the fastest and the tablets with the 54mg weight gain released the slowest from the 6 different weight gains that were tested.

[0754] Dissolution using USP3 was also conducted on this trial, using the tablet with the 52mg weight gain. The dissolution profile was plotted as time in hours versus % Dissolved, and was plotted alongside the in vivo data and the Bupropion HCl data in order for a comparison to be

made. The results (Figure 40) showed that the trial did not match the in vivo data, nor did it match the Bupropion HCl data.

[0755] Study on Batch BUP-HBr-EA-150mg-002-5

[0756] Using 150mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0757] The materials used in the Ethocel (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 59.

[0758] The parameters are as follows: Spray Rate: 14 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C ± 2°C; and Supply Air Flow: 200 CFW.

[0759] The coating process of this trial took 4 hours and 38 minutes to obtain a 36mg weight gain. Tablet weights were taken and recorded in Table 60 at 18mg, 20mg, 22mg, 24mg, 26mg, 28mg, 30mg, 32mg, 34mg and 36mg weight gains.

[0760] The dissolution profile (Figure 41) shows that the tablets with the 18mg and 20mg weight gains of EC coating released the fastest of all the weight gains tested. It was the tablets with the 36mg weight gain that released the slowest when compared to all the other weight gains.

Study on Batch BUP-HBr-EA-300mg-003-5

[0761] Using 300mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0762] The materials used in the Ethocel (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 61.

[0763] The parameters are as follows: Spray Rate: 14 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C ± 2°C; and Supply Air Flow: 200 CFW.

[0764] It took 4 hours and 13 minutes to add a 54mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains and were recorded in Table 62.

[0765] The dissolution profile (Figure 42) shows that the tablets with the 52mg weight gain of EC coating released the slowest when compared to the other profiles with different weight gains.

[0766] Study on Batch BUP-HBr-EA-300mg-004-5

[0767] Using 300mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0768] The materials used in the Ethocel (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 63.

[0769] The parameters are as follows: Spray Rate: 14 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C ± 2°C; and Supply Air Flow: 200 CFW.

[0770] It took 4 hours and 13 minutes to add a 54mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains and were recorded in Table 64.

[0771] The dissolution profile (Figure 43) shows that the tablets with the 52mg weight gain released the slowest when compared to the other profile and the tablets with the 44mg weight gain of EC coating released the fastest.

[0772] Study on Batch BUP-HBr-EA-300mg-005-5

[0773] Using 300mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0774] The materials used in the Ethocel (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 65.

[0775] The parameters are as follows: Spray Rate: 14 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C ± 2°C; and Supply Air Flow: 200 CFW.

[0776] It took 4 hours and 14 minutes to add a 54mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains and were recorded in Table 66.

[0777] Figure 44 shows that the tablets with the 54mg weight gain released the slowest when compared to the other profiles and that the tablets with the 44mg weight gain of EC coating released the fastest of the six profiles.

Study on Batch BUP-HBr-EA-150mg-006-5

[0778] Using 150mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0779] The materials used in the Ethocel (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 67.

[0780] The parameters are as follows: Spray Rate: 14 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50°C; Product Temperature: 35°C ± 2°C; and Supply Air Flow: 200 CFW.

[0781] The coating process of this trial took 4 hours and 36 minutes to obtain a 36mg weight gain. Tablet weights were taken and recorded in Table 68 at 18mg, 20mg, 22mg, 24mg, 26mg, 28mg, 30mg, 32mg, 34mg and 36mg weight gains.

[0782] The dissolution profile (Figure 45) shows that the tablets with the 36mg weight gain of EC coating released the slowest when compared to the other four profiles (24mg, 28mg, 32mg and 34mg weight gains).

[0783] Dissolution using USP3 was also conducted with this trial, in order to see if the results were close to the in vivo data and the in vitro data of the Bupropion HCl 300mg target. The dissolution profile (Figure 46) shows that the 150mg Bupropion HBr EA tablets with 24mg weight gain was close to the in vivo profile.

Study on Batch BUP-HBr-EA-150mg-007-5

[0784] Using 150mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0785] The materials used in the Ethocel (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 69.

EXAMPLE 7: COMPARATIVE FORCED DEGRADATION STUDIES ON BUPROPION HCL AND BUPROPION HBR DRUG PRODUCTS

[0786] The Bupropion HCl and HBr tablets (EC coated and the EC + moisture barrier coated) were placed individually on an open dish, and exposed to the accelerated conditions of 40°C/75%RH in the stability chamber. After 13 and 20 days, the samples were assayed and impurity analysis was performed as per the method HPLC P05.901.10.

[0787] Table 70 and Figure 47 show the 13 and 20 days results of the forced degradation study on both Bupropion HCl and HBr EC coated tablets. For the Bupropion HCl product, the main degradation impurities 3-CBZ and 852U77 were 0.12% and 0.38% respectively, whereas, for the Bupropion HBr, these values were 0.07% and 0.49% respectively. The other degradation

impurities and the total unknowns were very similar for both products; however, the assay value for the HBr product was higher than the HCl. The difference in the assay and the impurity levels were more significant in the final drug products. As shown in the Table 71 and Figure 48, for the same period of the study the assay of the Bupropion HCl was lower (95.5%) and the level of the degradation and total unknowns were higher (3-CBZ: 0.28%, 852U77: 1.23%, 827U76: 0.10% and total 1.73%) than the Bupropion HBr (3-CBZ: 0.12%, 852U77: 0.41%, 827U76: 0.05% and total 0.75%).

EXAMPLE 8: FURTHER FORCED DEGRADATION STUDIES ON BUPROPION HBR AND BUPROPION HCL IN THE PRESENCE OF EXCIPIENTS

[0788] Further forced degradation studies were carried out at 55oC, at 55oC and 100% relative humidity, at 100oC, and at 105 oC on both the HCl and HBr Bupropion salts in the presence of excipients. The average weight of the excipients and the weight of the active pharmaceutical ingredient (API) present in the samples are presented in Table 72. The results from this study are presented in Figures 49-53. Figure 49 shows the amount of 3-CBA impurity in the various samples. Figure 50 shows the amount of 852U77 impurity in the various samples. Figure 51 shows the amount of 20U78 impurity in the various samples. Figure 52 shows the amount of 827U76 impurity in the various samples. Figure 53 is a graph showing the loss of each salt over time in a TGA experiment at 100 oC. These results indicate that at elevated temperatures, a disproportionation of the HCl salt occurs with concomitant loss of gaseous HCl. This disproportionation did not occur with the HBr salt.

[0789] It is clear from the results that bupropion HBr shows significant improvements in stability compared to bupropion HCl. The degradation of bupropion HBr was slower as indicated by the formation of less amounts of impurities compared to bupropion HCl.

EXAMPLE 9: PREPARATION OF FURTHER BUPROPION HBR EA TABLETS

[0790] Using procedures as described in Example 6, further bupropion EA tablets were prepared using the quantities listed in Table 73.

EXAMPLE 10: ACCELERATED STABILITY STUDY OF BUPROPION HBR

[0791] The stability of bupropion HBr was evaluated under the accelerated conditions of 40 oC + 2 oC and 75% + 5% RH in a stability chamber. The samples were prepared in closed bottles and placed in the stability chamber. HPLC analysis was conducted on the samples prior to placing them in the stability chamber (time 0), and after 3 months and 6 months. The amounts of

the main degradation products present at time 0 were compared with those amounts present after 3 months and 6 months. As shown in Table 74 -76 three different batches of bupropion HBr were tested. For each sample tested, at each time period, two different HPLC assays were run. The first assay labelled chromatographic purity A, measured the percentage of three impurities 3'chloropropiophenone, 3'-Chloro-2-bromopropiophenone and 3'-Chlorobenzoic acid. The second assay, labelled chromatographic purity B, measured the percentage of 2-N-(tert-Butyl)-aminopropiophenone, a single unknown impurity and the total unknown impurities. Finally a total percentage of impurities (known and unknown) was reported for each sample. From the data presented it can be seen that there is a slight increase in the impurity 3'-chloropropiophenone. While slight fluctuations were seen in the percentage of other impurities there was no trend showing an increase of these impurities at the 3- and 6-month time periods as measured. The total percentage of impurities for each of the HBr samples did not change at either the 3-month or the 6-month time periods. These results indicate that the HBr salt of bupropion was highly stable under the accelerated stability test conditions.

EXAMPLE 11: SHELF LIFE STABILITY PROGRAM

[0792] The stability of bupropion HBr was studied over a longer term under conditions meant to approximate standard storage or shelf conditions. Samples were prepared in closed containers and subjected to long-term storage at 25oC + 2 oC and 60% + 5% RH in a stability chamber. The samples were analyzed by HPLC prior to being placed in the stability chamber (time 0) and after 3 months and 6 months. The amounts of the main degradation products present at time 0 were compared with the amounts present at 3 months and 6 months. As shown in Table 77-79 three different batches of bupropion HBr were tested. As in Example 10 each sample was tested under two HPLC assay conditions to identify 6 impurities or groups of impurities as described in Example 10. From the results shown in tables 77-79 it can be seen that the percentage of the impurity 3'-chloropropiophenone increased slightly over time. While the other impurities fluctuated slightly they did not show an increasing trend over time. These results demonstrate the stability of bupropion HBr under standard shelf conditions over an extended period of time.

EXAMPLE 12: PREPARATION AND STABILITY STUDY OF BUPROPION HBR POLYMORPHIC FORMS I, II AND III.

[0793] Bupropion hydrobromide polymorphic forms I, II and III were prepared in the following manner and their stability was studied under the conditions described below:

Form I:

[0794] A 250 ml flask equipped with overhead stirrer and gas inlet was charged with 34 g of bupropion base and 138 ml of isopropanol. The solution was maintained under stirring while 13g of gaseous HBr was introduced through the gas inlet in a time of 20' while the internal temperature of the mixture raises from 25 to 40oC. During the gas addition a heavy white precipitate formed. At the end of the gas addition the temperature of the mixture was raised to reflux (80oC), to get complete solution of the suspended solid. The temperature was then lowered to 25oC in 1 hour and further lowered to 0-5oC in 1 additional hour. The precipitate obtained was filtered and washed with 20 ml of cold isopropanol. The discharged wet solid was dried under vacuum (30mmHg) in a static drier at 50oC for 16 hours. 34 g of bupropion hydrobromide form I were obtained.

[0795] Samples of bupropion HBr form I were subjected to the conditions for the accelerated stability study as described in Example 10 and the shelf life stability study as described in Example 11. PXRD studies carried out after 3 months and 6 months for each sample gave the same results. The PXRD profile of one of the samples after 6 months in the accelerated stability condition is provided in figure 60.

Form II:

[0796] 10 g of bupropion HBr form I were dissolved in a mixture of 170ml of acetone and 7 ml of water. The mixture was brought to reflux with dissolution of the solid. The solution was then cooled to room temperature. After one night the precipitate formed was filtered and dried at 40oC under vacuum (30 mmHg) for 12 hours. 2.4 g of bupropion HBr form II were obtained. A sample of the product was prepared for an accelerated stability test, in ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) conditions (40 oC/75%r.h.), by sealing the product in polyethylene bags, which in turn were placed in aluminium bags containing silica and sealed and placed in the stability chamber in ICH conditions (40 oC/75%r.h.). The crystalline form was checked after maintaining the product under these conditions for 1 month. The PXRD profile shown in figure 61 shows that the compound is still in form II. This demonstrates the stability of crystal form II under these conditions.

Form III:

[0797] 20 g of bupropion hydrobromide form I and 96 ml of absolute ethanol were placed in a 250 ml flask. The mixture was brought to reflux obtaining complete dissolution of the solid. The solution was then cooled to room temperature without stirring and left in these conditions for 18 hours. The resulting crystalline solid was then filtered and dried under vacuum (30mmHg) at 50oC for 4 hours. 11.2 g of bupropion HBr form III were obtained. A sample of the product was prepared for stability testing by sealing the product in polyethylene bags, which in turn were placed in aluminium bags containing silica and sealed, and placed in the stability chamber in ICH conditions (40 oC/75%r.h.). The crystalline form was checked after maintaining the product in these conditions for 1 month. The PXRD profile shown in figure 62 demonstrates that the product is not stable in this form under these conditions, as the majority of the product changed to form II.

EXAMPLE 13: HBr – SR Tablets for 100 and 150 mg strength as alternate to HCl – SR

[0798] Formulation to be based on options used during the development of the Wellbutrin HCl SR 100 and 150 mg.

[0799] Bupropion HCl was replaced with HBr and adjusted to obtain same amount Bupropion base.

[0800] Filler materials adjusted accordingly in order to obtain the same tablet core weights.

e.g. 150 mg HCl = 130 mg base = 174 mg HBr

100 mg = 86.7 = 116

HBr granulation process:

[0801] Bupropion HBr is granulated with an aqueous solution containing Polyvinyl Alcohol and Stabilizing agent such as Oxalic acid or Succinic acid or Aspartic acid or other suitable acid compounds, in a Fluid bed granulator.

[0802] The dry granules are than mixed with water soluble polymer or mixtures of hydrophobic/hydrophilic polymers at various viscosity grades. In trials used Hypromellose (Hydroxypropyl methylcelluloseK4M CR grade) as well as Hydroxypropyl Cellulose (HPC) at quantities to obtain target release.

[0803] Microcrystalline Cellulose (MCC) was used as filler and binding material. Could be replaced with Lactose. For final lubrication Glyceryl Behenate (Compritol 888 ATO) was used. Other suitable lubricant such as Stearic Acid, Sodium Fumarate are suitable.

[0804] The compressed tablets are then coated with a non-functional colored film coating solution.

[0805] Formulation example: mg/unit (Target weight 400 mg) for 174 mg strength (equivalent to 150 mg HCl)

Bupropion HBr	174 mg
Polyvinyl Alcohol	16
Stabilizer	20
HPMC (HPC)	40
MCC	144
Glyceryl Behenate	6

Coating: Opadry provided by Colorcon, approximately 3-4 % weight gain

Above formulation(s) are evaluated without use of stabilizers.

EXAMPLE 14: FURTHER STABILITY STUDIES:

Stability of Bupropion HBr 348 Mg Tablets

[0806] In these studies, the stability of bupropion HBr tablets (Lot # Bup-HBr-XL-348-025-5 (7, 30 and 90 counts) were tested after storage at 40 degrees C and 75% relative humidity as described previously for 348 mg tablets prepared as described above and having the tablet composition shown in Table 99. These experiments evaluated the results of accelerated stability of the bupropion HBr XL 348 mg tablets packaged in 7, 30 and 90 counts based on a comparison of the changes in physical appearance, assay, the level of the known degradation impurities and the dissolution profiles of the 1, 2, 3 and 6M time points within the initial data.

[0807] No significant changes were observed in physical appearance, and the assay values of the tablets for all counts, however, as expected, there were gradual increase in the levels of two major known degradation impurities (3-CBZ and 852U77) and going from 7 to 90 counts, the percentages of the latter two impurities were varied. The dissolution profiles of the drug product for all counts were lower at the first month for all time points in comparison with the initial profile, however, other stability time points varied, for example:

[0808] 7 Counts: the 2M and 3M were similar to the initial and 6M similar to the 1M.

[0809] 30 Counts: The 6M was similar to the 1M and lower than the initial, the 2 & 4 hours time points for 2M and 3M were similar to the initial, however, the 8 & 16 hours time points were lower than the corresponding values.

[0810] 90 Counts: Essentially lower dissolution profiles were observed for 2M, 3M, and 6M in comparison with the initial profiles These results are contained in Figure 63.

EXAMPLE 15: ADDITIONAL STABILITY TESTING OF 150 mg, 300 mg Bupropion HBr Tablets (Lot # Bup-Hbr-Ea-150-002-5 and Bup-Hbr-300-001-5)

[0811] The same criteria were used to evaluate the stability of Bupropion HBr EA 150 and 300 mg drug products for the 90 counts. Similar results were obtained for the two drug products as compared with the bupropion HBr XL 348 XL 348 mg tablet-90 counts, however, better disolution stability data were observed, i.e., no significant differences of the dissolution profiles for 1M, 2M, 3M, & 6M were observed for the two EA products in comparison with their corresponding initials, except the 6M dissolution data for the 300 mg which showed slightly lower values. These results are in Figure 64.

EXAMPLE 16: Additional Open Dish-Closed Bottle Stability Studies

[0812] Experiments were conducted comparing the stability of bupropion HBr XL 174 mg core , Bupropion HBr XL 348 core, Bupropion HCl XL 150 mg Core and Bupropion HCl XL 300 mg core over 10 and 20 days under open bottle and closed bottle conditions. These studies were again effected at 40 degrees C and 75 % relative humidity. Degradation was again assessed by assaying for known impurities 3-CBZ and 852U77. As before the bupropion HBr cores were less subject to degradation than the bupropion HCl cores under open and closed bottle conditions. These results are contained in Figure 65.

EXAMPLE 17: DISSOLUTION OF BUPROPION FORMULATIONS ACCORDING TO THE INVENTION IN DIFFERENT USP-3 MEDIA

[0813] The dissolution of bupropion HBr formulations according to the invention were assessed in three USP-3 media, i.e., SGF pH 1.2, Acetate Buffer pH 4.5 and Phosphate Buffer pH 6.8 over a period of 16 hours. These results are contained in Figure 66. Particularly Bupropion HBr XL 348 mg tablets (final), Lot # Bup-HBr-XL-012-5; Wellbutrin XL 300 mg tablets (final), Lot # 05A116; Bupropion HBr XL 348 mg tablets ECl Lot # Bup-HBr-XL-012-5 (EC 32 mg wg) and Wellbutrin XL 300 mg tablets (ECl0-Lot # 05D047 were assessed in SGF media pH 1.2 for 2

hours, Acetate Buffer pH 4.5 for 2 hours, and Phosphate Buffer SIF pH 6.8 for a total of 10 hours. The results are contained in the Figure 66-68.

[0814] Additionally, Figure 66 contains the results of dissolution testing of a bupropion HBr formulation according to the invention, i.e., bupropion HBr 348 mg, lot # 05E304, versus BupHCl 300 mg (Bup 300XL Target) lot# 01L238 in vivo and BUP 300XL Target in USP3-0.5% SLS media over times ranging from 0 to 16 hours.

[0815] Additionally the same Figure tabulates the results of these dissolution experiments comparing % drug release over time for bupropion HBr 348 mg Lot # 05E304 in USP-3 media (SGF pH 1.2 and 0.5% SLS after 2 hours, Acetate Buffer pH 4.5 after 2 hours and Phosphate Buffer pH 6.8 after a total of 16 hrs.

[0816] Also, Figure 68 contains comparative dissolution profiles for Bupropion HBr XL 348 mg final ,Wellbutrin XL EC , tablets in different USP-3 media (SGF pH 1.2, acetate buffer pH 4.5 and phospate buffer pH 6.8) compared against in vivo data for Bupropion HCl 150 mg XL target (Lot 02A063) over a period of 16 hours.

Table 1: Assay of bupropion salts by HPLC

Test	Maleate	Tosylate	Fumarate	HBr	Succinate	Tartrate acid	Tartrate neutral	Citrate
Assay	99.7%	97.4%	89.8%	99.7%	97.6	84.9%	51.7%*	85.0%

Table 2: moisture content and pH of aqueous solutions:

Sample ID	Original (Initial APIs)		After re crystallization (R&D)		
			Tested after 1 day		Tested after 2 Months
	KF	pH (aq. 0.5%)	KF	pH (aq. 0.5%)	KF
Bup-HCl	0.0	5.90			
Bup-Maleate	0.10	4.29			
Bup-Tosylate	1.71*	5.56	023	5.88	0.18
Bup-Fumarate	0.09	3.84			
Bup-HBr	0.00	5.92			
Bup-Succinate	0.13	4.82			
Bup-Tartrate	0.18	3.62			
Bup-Tartrate neutral	0.14	3.62			
Bup-Citrate (I)	0.23	3.89			

* KF after 3M= **1.80%**

Bup = bupropion

Table 3: Solubility & other physical properties:Bupropion HBr vs Bupropion HCl.

Sample ID	Solubility (mg/ml)		
	Water	EtOH	IPA
Bupropion HCl	270	80	10
Bupropion HBr	143	92	12

Sample ID	PS (Malvern)	Moisture Content (KF)	pH (aq. 0.5%)	MP (DSC)
Bupropion HCl (Erregierre)	10% 32 µm 50% 102 µm 90% 276 µm	0.01%	5.90	243.6C
Bupropion HBr (Chemi)	10% 72 µm 50% 245 µm 90% 657 µm	0.00%	5.92	234.1C

Table 4:

40°C/75%RH			
Close Vial			
(DS + Placebo)[1]	(DS + Placebo)[1] + Water[2]	(DS + Placebo)[1] + (Water + EtOH + IPA)[3]	(DS + Placebo)[1] + (IPA+ EtOH)[4]

[1] 300mg of the drug substance was placed in a 2mL vial, then 100mg placebo (almost double of the required amount) was added, and mixed well.
[2] Two drops of water was added to the spiked placebo and mixed well with a spatula, then closed with a cup.
[3] A mixture of equal volume of water, EtOH and IPA was prepared. Two drops of the latter mixture was added to the spiked placebo, and mixed well with a spatula, then closed with a cup.
[4] A mixture of equal volume of EtOH and IPA was prepared. Two drops of the latter mixture was added to the spiked placebo, and mixed well with a spatula, then closed with a cup.

Table 5:

API ID	Lot#	Quantity/bottle	# of glass bottle 40°C/75%RH	Stability pulling time (Day)
Bupropion HBr	STN07492	348mg	2	14 & 24
Bupropion HCl	STN06973	300mg	2	14 & 24
Bupropion HBr	STN07491	348mg	1	10
	STN07492	348mg	1	10
Bupropion HCl	STN06973	300mg	1	10
	STN06978	300mg	1	10

Table 6: Closed glass bottle stability studies (40°C/75%RH) on Bupropion-HBr & HCl APIs.

Tests	Initial	Bupropion HBr, Lot# STN07492		Initial	Bupropion HCl, L# STN06973	
		14-Days	24 Days		14-Days	24 Days
%Assay	99.6	98.8	99.5	100.4	98.5	98.5
%Impurities 3-CBZ	0.007	0.015	0.022	0.002	0.019	0.082
852U77	0.009	0.058	0.052	0.003	0.010	0.023
20U78/dilu	0.044	0.048	0.038	0.045	0.038	0.040
827U76	ND	0.012	0.016	ND	ND	0.102
Total unknown	0.098	0.105	0.104	0.044	0.038	0.049
Total (%)	0.16	0.23	0.23	0.09	0.11	0.30

Table 7: Closed glass bottle stability studies (40C/75%RH) on Bupropion HCl & Bupropion HBr APIs.

Tests	Initial	Bupropion HBr, Lot# STN07491	Initial	Bupropion HBr, Lot# STN07492
		10-Days		10 Days
%Assay	99.5	98.2	99.6	99.2
%Impurities 3-CBZ	0.011	0.070	0.007	0.031
852U77	ND	0.125	ND	0.055
20U78/dilu	0.041	0.051	0.041	0.044
827U76	ND	0.039	ND	ND
Total unknown	0.129	0.129	0.194	0.15
Total (%)	0.17	0.42	0.23	0.24
Tests	Initial	Bupropion HCl, Lot# STN06973	Initial	Bupropion HCl, Lot# STN06978
		10-Days		10 Days
%Assay	99.4	96.3	99.1	96.5
%Impurities 3-CBZ	0.003	0.110	0.002	0.278
852U77	ND	0.047	ND	0.124
20U78/dilu	0.040	0.047	0.04	0.057
827U76	ND	0.045	ND	0.141
Total unknown	0.053	0.187	0.165	0.137
Total (%)	0.10	0.44	0.21	0.74

Table 8: Each trial's contents and amounts of each material per part

Materials	Amount (g)				
	Part 1	Part 2	Part 3	Part 4	Part 5
Bupropion HBr	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

Table 9: Summary of specifications 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

Table 10: 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 2	2131.25
Part 3	2131.25
Part 4	2131.25
Part 5	2131.25
Compritol 888	343.75
Total	11000.0

Table 11: Summary of Specifications for Tablet Press Set-up.

Parameters	Settings/Ranges
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

Table 12: Summary of specifications for compression

Parameters	Specification for 174mg Tablet	Specification for 348mg Tablet
Individual Tablet Weight (mg)	185.6 ± 5% (176.3mg-194.9mg)	371.2 ± 5% (352.6mg-389.8mg)
Average Tablet Weight (mg)	185.6 ± 3% (180.0mg-191.2mg)	371.2 ± 3% (360.1mg-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 13: Formulations used as the Ethocel coating on the 174mg and 348mg Bupropion HBr cores.

FORMULATION 1	FORMULATION 2	FORMULATION 3
- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Polyethylene Glycol 4000 - Ethyl Alcohol 95% USP - Isopropyl Alcohol (IPA)	- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Polyethylene Glycol 4000 - Dibutyl Sebacate - Ethyl Alcohol 95% USP	- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Polyethylene Glycol 4000 - Ethyl Alcohol 95% USP

Table 14: Formulations used as the Final Coats on the 174mg and 348mg Bupropion HBr tablets.

FORMULATION A	FORMULATION B
- Eudragit L30D-55 - Chroma-Tone DEB 5156-CLE - Purified Water	- Eudragit L30D-55 - Syloid 244FP - Polyethylene Glycol 4000 - Triethyl Citrate - Purified Water

Table 15: Summary of Specifications that were kept constant in the Ethocel coating Process.

Process Parameters	Operational Ranges	Target
Inlet Temperature for coating (°C)	SV: 40 ± 5 PV: 40 ± 5	40
Inlet Temperature for Drying (°C)	30-35	35
Exhaust Temperature	30 ± 10	30
Product Temperature	25-35	28
ΔP 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 16: Summary of Specifications that were kept constant in the Final coating Process.

Process Parameters	Operational Ranges	Target
Inlet Temperature for coating (°C)	SV: 50 ± 5	50
	PV: 50 ± 5	
Inlet Temperature for Drying (°C)	40 ± 5	40
Exhaust Temperature	35 ± 5	38
Product Temperature	35 ± 2	35
ΔP Differential Pressure (W.C)	(-0.1)-(-0.12)	-0.10
Supply Air Flow (CFM)	200 ± 50	200
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 17: Materials used in one part of the batch, the percentage of each constituent, the amount per tablet and the amount per batch, for BUP-HBr-XL-009-5

Materials	%	mg/tablet	Batch Quantity (g)
Bupropion HBr	93.75	348.00	1993.75
PVA	3.125	11.60	68.75
Compritol 888	3.125	11.60	68.75
Total	100.00	371.2mg	2131.25

Table 18: Results obtained using 9mm tooling for batch BUP-HBr-XL-009-5.

Parameters	Theoretical	Actual
Average Individual Tablet Weight	371.2mg	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%

Table 19: Results obtained using 10mm tooling for batch BUP-HBr-XL-009-5.

Parameters	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
Friability	<0.8%	0%

Table 20: Materials used in one part of the 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)
Bupropion HBr	93.75	174.00	1993.75
PVA	3.125	5.80	68.75
Compritol 888	3.125	5.80	68.75
Total	100.00	185.60	2131.25

Table 21: Results obtained using 7mm tooling for batch BUP-HBr-XL-021-5.

Parameters	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 22: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-348-013-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.60	77.44*	38.74
Povidone USP (Kollidone 90F)	4.600	99.22*	49.64
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 of the formulation included 77.44g of Ethocel, 99.22g of Povidone and 23.23g of PEG 4000, which gave a total solid amount of 199.89g. The solid component of the formulation made up 9% of the total solution and the remaining 91% was made up of liquid.

Table 23: Theoretical and Actual Tablet weights at 28mg, 30mg, 32mg and 34 mg weight gains for batch BUP-HBr-XL-348-013-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (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

Table 24: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-348-013-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	Amount of Solid (g)	% of Solids in Solution
Eudragit L30 D-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 of Eudragit, solid, that contributed to the total amount of solid was 65%.
**The percentage of Chroma-Tone, solid, that contributed to the total amount of solid was 35%.
***The Total amount of solid (48.34g) was 10.5% of the total solution.

Table 25: 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

Table 26: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-348mg-018-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.42	73.57	38.00
Povidone USP (Kollidone 90F)	4.41	94.86	49.00
PEG 4000	1.17	25.17	13.00
Ethyl Alcohol 95% 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 Ethocel, 94.86g of Povidone and 25.17g of PEG 4000. This gave a total of 193.6g total solid amount.

Table 27: Theoretical and Actual Tablet weights at 26mg, 28mg, 30mg, and 32mg weight gains for batch BUP-HBr-XL-348mg-018-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
26.0	398.0	397.7
28.0	400.0	399.5
30.0	402.0	401.5
32.0	404.0	404.0

Table 28: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-348mg-018-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	Amount of Solid (g)	% of Solids in Solution
Eudragit L30D D-55	22.75	104.86	31.46	65.00*
Syloid 244FP	2.62	12.08	12.08	25.00**
Carbowax 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 Eudragit, solid, that contributed to the total amount of solid was 65%.
**The percentage of Syloid, Carbowax 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 35%.
***The total amount of solid (48.4g) was 10.5% of the total solution.

Table 29: 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

Table 30: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-174mg-022-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.60	116.12	40.00
Povidone USP (Kollidone 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% USP	4.55	146.76	N/A
Total	100.00	3225.60	100.00

*Total Solid included 116.12g of Ethocel, 139.34g of Povidone and 34.84g of PEG 4000. This gave a total solid amount of 290.3g.

Table 31: Theoretical and Actual Tablet weights at 20mg, 22mg, 24mg, 26mg, 28mg, 29mg, and 30mg weight gains for batch BUP-HBr-XL-174mg-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 32: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-174mg-022-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	Amount of Solid (g)	% of Solids in Solution
Eudragit L30D D-55	22.75	104.86	31.46	65.0*
Syloid 244FP	2.62	12.08	12.08	25.0**
Carbowax 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 Eudragit, solid, that contributed to the total amount of solid was 65%.
**The percentage of Syloid, Carbowax 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 35%.
***The Total amount of solid (48.4g) was 10.5% of the total solution.

Table 33: Theoretical and Actual Tablet weights at 4mg, 5mg, 6mg, and 7mg weight gains for batch BUP-HBr-XL-174mg-022-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (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

Table 34: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-348mg-023-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.69	79.37	42.71
Povidone USP (Kollidone 90F)	3.69	79.37	42.71
PEG 4000	1.26	27.11	14.58
Dibutyl Sebacate, NF	0.36	7.75	N/A
Ethyl Alcohol 95% USP	91.00	1957.4	N/A
Total	100.00	2151.00	100.00

*Total Solid includes 79.37g of Ethocel, 79.37g of Povidone, 27.11g of PEG 4000 and 7.75g of Dibutyl Sebacate. This gave a total solid amount of 193.6g.

Table 35: Theoretical and Actual Tablet weights at 26mg, 28mg, 30mg, and 32mg weight 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 36: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-348mg-025-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.69	79.40	41.00
Povidone USP (Kollidone 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

* Total Solid included 79.40g of Ethocel, 81.30g of Povidone and 32.90g of PEG 4000. This gave a total solid amount of 193.6g.

Table 37: Theoretical and Actual Tablet weights at 26mg, 28mg, 30mg, and 32mg weight gains for batch BUP-HBr-XL-348mg-025-5.

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 38: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-348mg-025-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	Amount of Solid (g)	% of Solids in Solution
Eudragit L30D D-55	19.77	91.13	27.34	56.50*
Syloid 244FP	3.15	14.52	14.52	30.00**
Carbowax 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

* The percentage of Eudragit, solid, that contributed to the total amount of solid was 65%.
**The percentage of Syloid, Carbowax 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 of solid (48.39g) was 10.5% of the total solution.

Table 39: 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
7.0	411.0	411.1

Table 40: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-348mg-026-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.69	79.37	41.00
Povidone USP (Kollidone 90F)	3.69	79.37	41.00
PEG 4000	0.36	7.75	4.00
Dibutyl Sebacate, NF	1.26	27.11	14.00
Ethyl Alcohol 95% USP	91.00	1957.4	N/A
Total	100.00	2151.00	100.00

* Total Solid included 79.37g of Ethocel, 79.37g of Povidone, 7.75g of PEG 4000 and 27.11g of Dibutyl Sebacate. This gave a total solid amount of 193.6g.

Table 41: Theoretical and Actual Tablet weights at 26mg, 28mg, 30mg, and 32mg weight gains for batch BUP-HBr-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

Table 42: Materials used in the EC coating and their quantities for batch BUP-HBr-XL-174mg-027-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solid in Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	3.69	138.87	41.00
Povidone USP (Kollidone 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 of Ethocel, 142.25g of Povidone and 57.58g of PEG 4000. This gave a total solid amount of 338.7g.

Table 43: Theoretical and Actual Tablet weights at 22mg, 24mg, and 26mg weight gains for 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 44: Materials used in the Final coating and their quantities for batch BUP-HBr-XL-174mg-027-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	Amount of Solid (g)	% of Solids in Solution
Eudragit L30D D-55	19.77	182.27	54.68	56.5*
Syloid 244FP	3.15	29.03	29.03	30.0**
Carbowax 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 Eudragit, solid, that contributed to the total amount of solid was 56.5%.
**The percentage of Syloid, Carbowax 4000 and Triethyl Citrate that contributed to the total amount of solid was 30.0%, 9.0% and 4.5%, respectively.
This gave a total of 43.5%.
***The Total amount of solid (9.77g) was 10.5% of the total solution.

Table 45: Theoretical and Actual Tablet weights at 4mg, 5mg, 6mg, and 7mg weight gains for batch BUP-HBr-XL-174mg-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

Table 46: Each trial's contents and amounts of each material per part for EA formulation.

Materials	Amount (g)				
	Part 1	Part 2	Part 3	Part 4	Part 5
Bupropion HBr	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

Table 47: Summary of specifications for granulation procedure for EA formulations.

Specification	Setting/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

Table 48: The amount of lubricant in the final EA formulation was 343.75g, which was 3.125% of the total.

Materials	Amount (g)
Bupropion HBr Granules	10656.25
Compritol 888	343.75
Total	11000

Table 49: Summary of Specifications for Tablet Press Set-up for the EA formulation.

Parameters	Settings/Ranges
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

Table 50: Summary of specifications for compression for the EA formulation.

Parameters	Specification for 150mg Tablet	Specification for 300mg Tablet
Individual Tablet Weight (mg)	160.0 ± 5% (152.0mg-168.0mg)	320.0 ± 5% (304.0mg-336.0mg)
Average Tablet Weight (mg)	160.0 ± 3% (155.2mg-164.8mg)	320.0 ± 3% (310.4mg-329.6mg)
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 51: Formulations used as the Ethocel coating on the 150mg and 300mg Bupropion HBr EA cores.

FORMULATION 1	FORMULATION 2	FORMULATION 3	FORMULATION 4
- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Polyethylene Glycol 4000 - Ethyl Alcohol 200 proof	- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Polyethylene Glycol 4000 - Dibutyl Sebacate - Ethyl Alcohol 200 proof	- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Dibutyl Sebacate - Ethyl Alcohol 200 proof	- Ethocel (Ethyl Cellulose) Standard 100 Premium - Povidone USP (Kollidone 90F) - Polyethylene Glycol 4000 - Ethyl Alcohol 95% USP

Table 52: Summary of Specifications that were kept constant in the Coating Process for the EA formulations.

Process Parameters	Ranges	Target
Inlet Temperature for coating (°C)	SV: 50 ± 5 PV: 50 ± 5	50
Inlet Temperature for Drying (°C)	40 ± 5	40
Exhaust Temperature	35 ± 5	35
Product Temperature	35 ± 2	35
ΔP Differential Pressure (W.C)	(-0.1)-(-0.12)	-0.10
Supply Air Flow (CFM)	200 ± 50	200
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

Table 53: Materials used in the batch, the percentage of each constituent, the amount per 300mg EA tablet and the amount per batch.

Materials	%	mg/tablet	Batch Quantity (g)
Bupropion HBr	93.75	300.00	1993.75
PVA	3.125	10.00	68.75
Compritol 888	3.125	10.00	68.75
Total	100.00	320.0mg	2131.25

Table 54: Materials used in the batch, the percentage of each constituent, the amount per 150mg EA tablet and the amount per batch.

Materials	%	mg/tablet	Batch Quantity (g)
Bupropion HBr	93.75	150.00	1993.75
PVA	3.125	5.00	68.75
Compritol 888	3.125	5.00	68.75
Total	100.00	160.0mg	2131.25

Table 55: Results obtained using 9mm tooling (EA formulations).

Parameters	Theoretical	Actual
Average Individual Tablet Weight	372.0mg	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%

Table 56: Results obtained using 7mm tooling (EA formulations).

Parameters	Theoretical	Actual
Average Individual Tablet Weight	372.0mg	366.5mg
Average Hardness	6.0-12.0 SC	7.50 SC
Average Thickness	5.0-6.0mm	4.97 mm
Friability	<0.8%	0%

Table 57: Materials used in the EC coating and their quantities for batch BUP-HBr-EA-300mg-001-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	185.62*	55.00
Povidone USP (Kollidone 90F)	2.52	94.50*	28.00
PEG 4000	0.77	28.69*	8.50
Dibutyl Sebacate	0.77	28.69*	8.50
Ethyl Alcohol Anhydrous (200 Proof)	91.0	3412.5	N/A
Total	100.00	3750.00	100.00

* Total solid component of the formulation included all the material except for the Ethyl Alcohol. This formulation consisted of a total solid amount of 337.5g, which made up 9% of the total solution. The remaining 91% was made up of the Ethyl Alcohol 200 proof (liquid).

Table 58: Theoretical and Actual EA Tablet weights at 44mg, 46mg, 48mg, 50mg, 52mg and 54mg weight gains for batch BUP-HBr-EA-300mg-001-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
44.0	364.0	362.9
46.0	366.0	365.6
48.0	368.0	366.6
50.0	370.0	369.3
52.0	372.0	371.7
54.0	374.0	374.8

Table 59: Materials used in the EC coating and their quantities for batch BUP-HBr-EA-150mg-002-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	232.03*	55.0
Povidone USP (Kollidone 90F)	2.52	118.12*	28.0
PEG 4000	0.77	35.86*	8.5
Dibutyl Sebacate	0.77	35.86*	8.5
Ethyl Alcohol Anhydrous (200 Proof)	91.0	4265.63	N/A
Total	100.00	4687.50	100.00

* Total solid included 232.03g of Ethocel, 118.12g of Povidone, 35.86g of PEG 4000 and 35.86g of Dibutyl Sebacate. This gave a total solid amount of 421.87g.

Table 60: Theoretical and Actual Tablet weights at 18mg, 20mg, 22mg, 24mg, 26mg, 28mg, 30mg, 32mg, 34mg, and 36mg weight gains for batch BUP-HBr-EA-150mg-002-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
18.0	178.0	178.2
20.0	180.0	181.0
22.0	182.0	181.8
24.0	184.0	184.3
26.0	186.0	185.8
28.0	188.0	188.1
30.0	190.0	190.7
32.0	192.0	192.5
34.0	194.0	193.7
36.0	196.0	195.5

Table 61: Materials used in the EC coating and their quantities for batch BUP-HBr-EA-300mg-003-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	185.62*	55.00
Povidone USP (Kollidone 90F)	2.52	94.50*	28.00
Dibutyl Sebacate	1.54	57.38*	17.00
Ethyl Alcohol Anhydrous (200 Proof)	91.0	3412.5	N/A
Total	100.00	3750.0	100.00

*Total Solid included 185.62g of Ethocel, 94.50g of Povidone and 57.38g of Dibutyl Sebacate. This gave a total solid amount of 337.5g.

Table 62. Theoretical and Actual Tablet weights at 44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains for batch BUP-HBr-EA-300mg-003-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
44.0	364.0	364.7
46.0	366.0	365.8
48.0	368.0	367.7
50.0	370.0	369.7
52.0	372.0	371.9
54.0	374.0	372.9

Table 63: Materials used in the EC coating and their quantities for batch BUP-HBr-EA-300mg-004-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	185.62*	55.00
Povidone USP (Kollidone 90F)	2.52	94.50*	28.00
PEG 4000	1.54	57.38*	17.00
Ethyl Alcohol Anhydrous (200 Proof)	91.00	3412.50	N/A
Total	100.00	3750.00	100.00

*Total Solid amount included 185.62g of Ethocel, 94.50g of Povidone and 57.38g of PEG 4000. This gave a total solid amount of 337.5g.

Table 64: Theoretical and Actual Tablet weights at 44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains for batch BUP-HBr-EA-300mg-004-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
44.0	364.0	363.6
46.0	366.0	365.5
48.0	368.0	368.5
50.0	370.0	370.2
52.0	372.0	372.6
54.0	374.0	374.3

Table 65: Materials used in the EC coating and their quantities for batch BUP-HBr-EA-300mg-005-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	185.62*	55.00
Povidone USP (Kollidone 90F)	2.52	94.50*	28.00
PEG 4000	0.77	28.69*	8.50
Dibutyl Sebacate	0.77	28.69*	8.50
Ethyl Alcohol Anhydrous (200 Proof)	91.00	3412.50	N/A
Total	100.00	3750.0	100.00

* Total Solids included 185.62g of Ethocel, 94.50g of Povidone, 28.69g of PEG 4000 and 28.69g of Dibutyl Sebacate. This gave a total solid amount of 337.50g. Therefore, solids made 9% contribution to the Total solution, and the remaining 91% was made up by the liquid component (Ethyl Alcohol Anhydrous).

Table 66: Theoretical and Actual Tablet weights at 44mg, 46mg, 48mg, 50mg, 52mg, and 54mg weight gains for batch BUP-HBr-EA-300mg-005-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
44.0	364.0	364.9
46.0	366.0	366.3
48.0	368.0	368.5
50.0	370.0	371.7
52.0	372.0	372.9
54.0	374.0	373.7

Table 67: Materials used in the EC coating and their quantities for batch BUP-HBr-EA-300mg-006-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids in Solution
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	232.03*	55.00
Povidone USP (Kollidone 90F)	2.52	118.12*	28.00
Dibutyl Sebacate	1.54	71.72*	17.00
Ethyl Alcohol Anhydrous (200 Proof)	91.0	4265.63	N/A
Total	100.00	4687.50	100.00

* Total solid included 232.03g of Ethocel, 118.12g of Povidone and 71.72g of Dibutyl Sebacate. This gave a total solid amount of 421.87g. The Solid component of the coating solution made up 9% of the total solution. The remaining 91% of the solution was made up by the Ethyl Alcohol Anhydrous (liquid component).

Table 68: Theoretical and Actual Tablet weights at 18mg, 20mg, 22mg, 24mg, 26mg, 28mg, 30mg, 32mg, 34mg, and 36mg weight gains for batch BUP-HBr-EA-150mg-006-5.

Weight Gain (mg)	Theoretical Weight (mg)	Actual Weight (mg)
18.0	178.0	178.2
20.0	180.0	180.3
22.0	182.0	181.8
24.0	184.0	184.6
26.0	186.0	185.8
28.0	188.0	188.8
30.0	190.0	190.9
32.0	192.0	191.6
34.0	194.0	194.1
36.0	196.0	196.7

Table 69. Materials used in the EC coating and their quantities for batch BUP-HBr-EA-150mg-007-5.

Materials	% Contribution to Total Solution	Batch Quantity (g)	% of Solids Solution*
Ethocel (Ethyl Cellulose) Standard 100 Premium	4.94	232.03	55.00
Povidone USP (Kollidone 90F)	2.52	118.12	28.00
PEG 4000	1.54	71.72	17.00
Ethyl Alcohol 95% USP	91.00	4265.63	N/A
Total	100.00	4687.50	100.00

* Total Solid included 232.03g of Ethocel, 118.12g of Povidone and 71.72g of PEG 4000. This gave a total solid amount of 421.87g.

Table 70: Open-dish stability studies (40C/75%RH) on Bupropion HCl & Bupropion HBr EC Coated Tablets

Tests	Initial	Open dish stability (40C/75%.RH)	
		13 Days	20 Days
Bupropion HBr XL 348mg coated EC tablets (EC-32mg WG.), Lot# Bup-HBr-XL-012-5 (EC-32mg wg.)			
%Assay	101.2	99.6	99.9
%Impurities			
3-CBZ	0.021	0.056	0.067
852U77	0.029	0.350	0.486
20U78/dilu	0.054	0.046	0.047
827U76	ND	0.056	0.062
Total unknown	0.356	0.059	0.123
Total	0.46	0.57	0.79
Bupropion HCl XL 300mg coated EC tablets (EC, Lot# 05D047)			
%Assay	100.4	100.2	96.2
%Impurities			
3-CBZ	0.015	0.089	0.117
852U77	0.041	0.337	0.378
20U78/dilu	0.038	0.046	0.045
827U76	0.023	0.071	0.080
Total unknown	0.118	0.112	0.145
Total	0.24	0.66	0.77

Table 71: Open dish-stability studies (40C/75%RH) on Bupropion HCl & HBr Final Coated Tablets

Tests	Initial	Bupropion HBr XL 348mg coated tablets (final 8mg wg), Lot# Bup-HBr-XL-012-5 (EC32mg wg- final 8mg wg.)		Initial	Wellbutrin (Bupropion HCl) XL 300mg tablets Lot# 05A116	
		13-Days	20 Days		13 Days	20 Days
%Assay	97.7	103.0	98.6	98.1	95.6	95.5
%Impurities 3-CBZ	0.021	0.091	0.119	0.032	0.171	0.279
852U77	0.039	0.505	0.412	0.193	0.974	1.228
20U78/dilu	0.051	0.055	0.048	0.042	0.055	0.062
827U76	ND	0.046	0.054	0.028	0.082	0.096
Total unknown	0.476	0.110	0.112	0.083	0.033	0.06
Total (%)	0.58	0.80	0.75	0.38	1.32	1.73

Table 72: Average weight of excipients and weight of the API present in the forced degradation samples for Example 8

Component	Average weight in mgs present in samples used for Forced deg study	
API	348 –HBr	350 - HCl
Precirol	162	
Mannitol	413	
Avicel pH101	154	
L-HPC	20	
Kollidon	20	
Citric acid	31	
Ethylcellulose E45	54	
ATBC	16	

TABLE 73: BUPROPION HBr EA COATING SOLUTION FORMULATION / mg /TABLET FOR PIVOTAL BATCHES

150mg EA Coated Tablets – Pivotal Coating Formulation / Batch Size				
Item #	Material	Qty. Required (kg)	% of Batch	Mg / tablet
RE0233	Ethylcellulose 100, NF	4.210	4.95%	19.80
RE0067	Povidone, USP	2.140	2.52%	10.06
RE0331	Polyethylene Glycol 4000, NF	0.435	0.51%	2.05
RE0103	Dibutyl Sebacate, NF	0.870	1.02%	4.09
RS0010	Dehydrated Alcohol, 200 proof, USP	73.475	86.44%	N/A
RS0006	Ethyl Alcohol, 95%, USP	3.870	4.56%	N/A
COOATING SOLUTION TOTAL (kg)		85 kg	100%	36 mg Range: (38-40mg)
*RE0223	Carnauba Wax, NF	0.010 kg	N/A	0.05 mg/tablet
300 mg EA Coated Tablets – Pivotal Coating Formulation / Batch Size				
Item #	Material	Qty. Required (kg)	% of Batch	Mg / tablet
RE0233	Ethylcellulose 100, NF	5.450	4.95%	23.12
RE0067	Povidone, USP	2.770	2.52%	11.75
RE0331	Polyethylene Glycol 4000, NF	0.560	0.51%	2.38
RE0103	Dibutyl Sebacate, NF	1.120	1.02%	4.75
RS0010	Dehydrated Alcohol, 200 proof, USP	95.070	86.43%	N/A
RS0006	Ethyl Alcohol, 95%, USP	5.030	4.57%	N/A
COATING SOLUTION TOTAL (kg)		110 kg	100%	42 mg / tablet Range: (40-44mg)
*RE0223	Carnauba Wax, NF	0.010 kg	N/A	0.05 mg/tablet

Note: Where applicable, percentages and mg/tablet totals have been rounded to two decimal places.

*Carnauba Wax not included as part of coating solution formulation. Trace amounts applied after completion of the coating process.

[0817] The patent and non-patent references cited in this patent specification are incorporated by reference in their entireties to the extent that their disclosures are not inconsistent with the explicit or implicit teachings of this application especially the definitions.

TABLE 74

ACCELERATED STABILITY PROGRAM					
Product: Bupropion.HBr FV0092	Batch No.: D00894	Start date: 20/12/04		Temperature: 40°C ± 2°C R.H.: 75% ± 5%	
Analysis	**Specification**	**time 0**	**3 month**	**6 months**	
Description	white or almost white crystalline powder	conform	conform	conform	
Identification	IR, HPLC (positive)	positive	positive	positive	
Water content (K.F.)	NMT 0.5 %	0.05	0.07	0.08	
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.	1) 0.05	
	2) NMT 0.1%	2) n.d.	2) n.d.	2) n.d.	
	3) NMT 0.1%	3) n.q.	3) n.q.	3) n.q.	
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03	4) 0.04	
	5) NMT 0.1%	5) 0.04	5) 0.04	5) n.q.	
	6) NMT 0.3%	6) 0.04	6) 0.06	6) 0.02	
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	
Assay (HPLC) on d.b.	98.0 - 102.0 %	99.6	99.6	99.7	

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).

Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

TABLE 75

ACCELERATED STABILITY PROGRAM				
Product: Bupropion.HBr FV0092	Batch No.: D00895	Start date: 20/12/04		Temperature: 40°C ± 2°C R.H.: 75% ± 5%
Analysis	**Specification**	**time 0**	**3 month**	**6 months**
Description	white or almost white crystalline powder	conform	conform	conform
Identification	IR, HPLC (positive)	positive	positive	positive
Water content (K.F.)	NMT 0.5 %	0.04	0.07	0.07
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.	1) 0.05
	2) NMT 0.1%	2) n.d.	2) n.d.	2) n.d.
	3) NMT 0.1%	3) n.q.	3) 0.05	3) n.q.
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03	4) 0.04
	5) NMT 0.1%	5) 0.04	5) 0.04	5) n.q.
	6) NMT 0.3%	6) 0.04	6) 0.05	6) 0.02
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1
Assay (HPLC)	98.0 - 102.0 % on d.b.	99.2	100.7	99.7

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).
Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

TABLE 76

ACCELERATED STABILITY PROGRAM					
Product: Bupropion.HBr FV0092	Batch No.: D00896		Start date: 20/12/04		Temperature: 40°C ± 2°C R.H.: 75% ± 5%
Analysis	**Specification**	**time 0**	**3 month**		**6 months**
Description	white or almost white crystalline powder	conform	conform		conform
Identification	IR, HPLC (positive)	positive	positive		positive
Water content (K.F.)	NMT 0.5 %	0.06	0.11		0.04
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.		1) 0.05
	2) NMT 0.1%	2) n.d.	2) n.d.		2) n.d.
	3) NMT 0.1%	3) n.q.	3) n.q.		3) n.q.
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03		4) 0.04
	5) NMT 0.1%	5) 0.05	5) 0.04		5) n.q.
	6) NMT 0.3%	6) 0.05	6) 0.05		6) n.q.
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1		0.1
Assay (HPLC)	98.0 - 102.0 % on d.b.	99.3	100.0		100.4
Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included). Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.					

TABLE 77

SHELF LIFE STABILITY PROGRAM											
Product: Bupropion.HBr FV0092	Batch No.: D00894		Start date: 20/12/04			Temperature: 25°C ± 2°C; Relative Humidity: 60% ± 5%					
Analysis	Specification	time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Description	white or almost white crystalline powder	conform	conform	conform	conform	conform			
Identification	IR, HPLC (positive)	positive	positive	positive	positive	positive			
Water content (K.F.)	NMT 0.5 %	0.05	0.05	0.06	0.05	0.05			
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.	1) 0.05	1) n.q.	1) n.d.	1)	1)	1)
	2) NMT 0.1%	2) n.d.	2) n.d.	2) n.d.	2) n.d.	2) n.d.	2)	2)	2)
	3) NMT 0.1%	3) n.q.	3) n.q.	3) n.q.	3) n.q.	3) 0.05	3)	3)	3)
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03	4) 0.05	4) n.d.	4) 0.05	4)	4)	4)
	5) NMT 0.1%	5) 0.04	5) 0.04	5) n.q.	5) n.q.	5) 0.05	5)	5)	5)
	6) NMT 0.3%	6) 0.04	6) 0.05	6) 0.02	6) n.q.	6) 0.07	6)	6)	6)
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	n.q.	0.2			
Assay (HPLC)	98.0 - 102.0% on d.b.	99.6	99.4	100.2	99.5	99.6			
Microbial cont.	• total microbial count < 1000 cfu/g	not applied	not applied	not applied	not applied	< 100 ufc/g	not applied		
	• moulds and yeast < 100 cfu/g					< 100 ufc/g			

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).

Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

TABLE 78

SHELF LIFE STABILITY PROGRAM									
Product: Bupropion.HBr FV0092	Batch No.: D00895		Start date: 20/12/04			Temperature: 25°C ± 2°C; Relative Humidity: 60% ± 5%			
Analysis	Specification	time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Description	white or almost white crystalline powder	conform	conform	conform	conform	conform			
Identification	IR, HPLC (positive)	positive	positive	positive	positive	positive			
Water content (K.F.)	NMT 0.5 %	0.04	0.04	0.05	0.05	0.04			
Chromatographic purity A) (HPLC)	1) NMT 0.1% 2) NMT 0.1% 3) NMT 0.1%	1) n.d. 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) 0.05 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) n.d. 2) n.d. 3) 0.05	1) 2) 3)	1) 2) 3)	1) 2) 3)
Chromatographic purity B) (HPLC)	4) NMT 0.1% 5) NMT 0.1% 6) NMT 0.3%	4) 0.04 5) 0.04 6) 0.04	4) 0.03 5) 0.04 6) 0.05	4) 0.05 5) n.q. 6) 0.02	4) n.d. 5) n.q. 6) n.q.	4) 0.05 5) 0.07 6) 0.07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	n.q.	0.2			
Assay (HPLC)	98.0 - 102.0% on d.b.	99.2	99.5	100.1	99.4	99.4			
Microbial cont.	• total microbial count < 1000 cfu/g • moulds and yeast < 100 cfu/g	not applied	not applied	not applied	not applied	< 100 ufc/g < 100 ufc/g	not applied		

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).
Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

TABLE 79

SHELF LIFE STABILITY PROGRAM									
Product: Bupropion.HBr FV0092	Batch No.: D00896		Start date: 20/12/04			Temperature: 25°C ± 2°C; Relative Humidity: 60% ± 5%			
Analysis	Specification	time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Description	white or almost white crystalline powder	conform	conform	conform	conform	conform			
Identification	IR, HPLC (positive)	positive	positive	positive	positive	positive			
Water content (K.F.)	NMT 0.5 %	0.06	0.04	0.04	0.04	0.03			
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.	1) 0.05	1) n.q.	1) n.d.	1)	1)	1)
	2) NMT 0.1%	2) n.d.	2) n.d.	2) n.d.	2) n.d.	2) n.d.	2)	2)	2)
	3) NMT 0.1%	3) n.q.	3) n.q.	3) n.q.	3) n.q.	3) n.q.	3)	3)	3)
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03	4) 0.04	4) n.d.	4) 0.05	4)	4)	4)
	5) NMT 0.1%	5) 0.05	5) 0.04	5) n.q.	5) n.q.	5) 0.07	5)	5)	5)
	6) NMT 0.3%	6) 0.05	6) 0.05	6) n.q.	6) n.q.	6) 0.07	6)	6)	6)
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	n.q.	0.1			
Assay (HPLC)	98.0 - 102.0% on d.b.	99.3	99.4	100.5	99.4	100.3			
Microbial cont.	• total microbial count < 1000 cfu/g • moulds and yeast < 100 cfu/g	not applied	not applied	not applied	not applied	< 100 ufc/g < 100 ufc/g	not applied		

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).
Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Table 80

Bupropion Hydrobromide Polymorphs Table

Trial	Solvent (voll.)	Cosolvent (voll.)	Yield (%)	Form	K. F. (%)	Notes
085	IPA + HBr gas			I	0.07	Standard procedure
097	Water 2	/	72	I	0.06	
098A	Methanol 2.4	/		II	0.13	
098B	Acetone 17	water 0.7	24	II	0.16	
099	Ethanol abs. 4.8	/	56	III	0.12	
100	IPA 15.1	/	77	I	0.11	
102	AcOi-Pr 20	MeOH 3.6	26	I	0.25	
108	Acetonitrile 20	/	70	I	0.14	
109	Dichloromethane 30	/	25	II	0.21	
110	Water 2	HBr 48% 1	83	I	0.12	
111	IPA 6	HBr 48% 1	69	I	0.32	
112	MTBE 10	MeOH 3	67	I	0.18	
113	Toluene 10	MeOH 1.25	40	II	0.39	
114	DMC 10	MeOH 1.75	67	II	0.17	
115	t-BuOH 20	Water 0.55	74	I	0.15	
116	Form I in rotavapor 100°C 24 h			I	0.45	
117	IPA 10	Water 0.125	88	I	0.32	
118	Toluene 10	MeOH 1.15	99	I	0.16	
119	IPA 8	MeOH 1.32	83	I	0.47	
120	Sec-BuOH 25	/	89	I	0.13	
122	Water 8	/		I	1.3	Spray dried

TABLE 81

Polyethoxylated Fatty Acids

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown here in Table 81.

PEG-Fatty Acid Monoester Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG 4-100 monolaurate	Crodet L series (Croda)	>9
PEG 4-100 monooleate	Crodet O series (Croda)	>8
PEG 4-100 monostearate	Crodet S series (Croda), Myrj Series (Atlas/ICI)	>6
PEG 400 distearate	Cithrol 4DS series (Croda)	>10
PEG 100, 200, 300 monolaurate	Cithrol ML series (Croda)	>10
PEG 100, 200, 300 monooleate	Cithrol MO series (Croda)	>10
PEG 400 dioleate	Cithrol 4DO series (Croda)	>10
PEG 400-1000 monostearate	Cithrol MS series (Croda)	>10
PEG-1 stearate	Nikkol MYS-IEX (Nikko), Coster KI (Condea)	2
PEG-2 stearate	Nikkol MYS-2 (Nikko)	4
PEG-2 oleate	Nikkol MYO-2 (Nikko)	4.5
PEG-4 laurate	Mapeg® 200 ML (PPG), Kessco® PEG 200ML (Stepan), LIPOPEG 2L (LIPO Chem.)	9.3
PEG-4 oleate	Mapeg® 200 MO (PPG), Kessco® PEG200 MO (Stepan),	8.3
PEG-4 stearate	Kessco® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6.5
PEG-5 stearate	Nikkol TMGS-5 (Nikko)	9.5
PEG-5 oleate	Nikkol TMGO-5 (Nikko)	9.5
PEG-6 oleate	Algon OL 60 (Auschem SpA), Kessco® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8.5
PEG-7 oleate	Algon OL 70 (Auschem SpA)	10.4
PEG-6 laurate	Kessco® PEG300 ML (Stepan)	11.4
PEG-7 laurate	Lauridac 7 (Condea)	13
PEG-6 stearate	Kessco® PEG300 MS (Stepan)	9.7

PEG-Fatty Acid Monoester Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-8 laurate	Mapeg® 400 ML (PPG), LIPOPEG 4DL(Lipo Chem.)	13
PEG-8 oleate	Mapeg® 400 MO (PPG), Emulgante A8 (Condea); Kessco PEG 400 MO (Stepan)	12
PEG-8 stearate	Mapeg® 400 MS (PPG), Myrj 45	12
PEG-9 oleate	Emulgante A9 (Condea)	>10
PEG-9 stearate	Cremophor 59 (BASF)	>10
PEG-10 laurate	Nikkol MYL-10 (Nikko), Lauridac 10 (Croda)	13
PEG-10 oleate	Nikkol MYO-10 (Nikko)	11
PEG-10 stearate	Nikkol MYS-10 (Nikko), Coster K100 (Condea)	11
PEG-12 laurate	Kessco® PEG 600ML (Stepan)	15
PEG-12 oleate	Kessco® PEG 600MO (Stepan)	14
PEG-12 ricinoleate	(CAS #9004-97-1)	>10
PEG-12 stearate	Mapeg® 600 MS (PPG), Kessco® PEG 600MS (Stepan)	14
PEG-15 stearate	Nikkol TMGS-15 (Nikko), Koster K15 (Condea)	14
PEG-15 oleate	Nikkol TMGO-15 (Nikko)	15
PEG-20 laurate	Kessco® PEG 1000 ML (Stepan)	17
PEG-20 oleate	Kessco® PEG 1000 MO (Stepan)	15
PEG-20 stearate	Mapeg® 1000 MS (PPG), Kessco® PEG 1000 MS (Stepan), Myrj 49	16
PEG-25 stearate	Nikkol MYS-25 (Nikko)	15
PEG-32 laurate	Kessco® PEG 1540 ML (Stepan)	16
PEG-32 oleate	Kessco® PEG 1540 MO (Stepan)	17
PEG-32 stearate	Kessco® PEG 1540 MS (Stepan)	17
PEG-30 stearate	Myrj 51	>10
PEG-40 laurate	Crodet L40 (Croda)	17.9
PEG-40 oleate	Crodet O40 (Croda)	17.4
PEG-40 stearate	Myrj 52, Emerest® 2715 (Henkel), Nikkol MYS-40 (Nikko)	>10
PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
PEG-50 stearate	Myrj 53	>10
PEG-55 stearate	Nikkol MYS-55 (Nikko)	18
PEG-100 oleate	Crodet 0-100 (Croda)	18.8
PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19
PEG-200 oleate	Albunol 200 MO (Taiwan Surf.)	>10
PEG-400 oleate	LACTOMUL (Henkel), Albunol 400 MO (Taiwan Surf.)	>10
PEG-600 oleate	Albunol 600 MO (Taiwan Surf)	>10

TABLE 82

PEG-Fatty Acid Diesters

Polyethylene glycol (PEG) fatty acid diesters are also suitable for use as surfactants in the compositions of the present invention. Representative PEG-fatty acid diesters are shown here in Table 82.

PEG-Fatty Acid Diester Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-4 dilaurate	Mapeg® 200 DL (PPG), Kessco® PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7 6
PEG-4 dioleate	Mapeg® 200 DO (PPG),	6
PEG-4 distearate	Kessco® 200 DS (Stepan)	5
PEG-6 dilaurate	Kessco® PEG 300 DL (Stepan)	9.8
PEG-6 dioleate	Kessco® PEG 300 DO (Stepan)	7.2
PEG-6 distearate	Kessco® PEG 300 DS (Stepan)	6.5
PEG-8 dilaurate	Mapeg® 400 DL (PPG), Kessco® PEG 400 DL (Stepan), LIPOPEG 4 DL (Lipo Chem.)	11
PEG-8 dioleate	Mapeg® 400 DO (PPG), Kessco® PEG 400 DO (Stepan), LIPOPEG 4 DO(Lipo Chem.)	8.8
PEG-8 distearate	Mapeg® 400 DS (PPG), CDS 400 (Nikkol)	11
PEG-10 dipalmitate	Polyaldo 2PKFG	>10
PEG-12 dilaurate	Kessco ® PEG 600 DL (Stepan)	11.7
PEG-12 distearate	Kessco® PEG 600 DS (Stepan)	10.7
PEG-12 dioleate	Mapeg® 600 DO (PPG), Kessco® 600 DO(Stepan)	10
PEG-20 dilaurate	Kessco® PEG 1000 DL (Stepan)	15
PEG-20 dioleate	Kessco® PEG 1000 DO (Stepan)	13
PEG-20 distearate	Kessco® PEG 1000 DS (Stepan)	12
PEG-32 dilaurate	Kessco® PEG 1540 DL (Stepan)	16
PEG-32 dioleate	Kessco® PEG 1540 DO (Stepan)	15
PEG-32 distearate	Kessco® PEG 1540 DS (Stepan)	15
PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
PEG-400 distearate	Cithrol 4DS series (Croda)	>10

TABLE 83

PEG-Fatty Acid Mono- and Di-ester Mixtures

In general, mixtures of surfactants are also useful in the present invention, including mixtures of two or more commercial surfactant products. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters. Representative surfactant mixtures are shown here in Table 83.

PEG-Fatty Acid Mono-and Diester Mixtures	
Compound	**Commercial Product (Supplier)**
PEG 4-150 mono, dilaurate	Kessco® PEG 200-6000 mono, dilaurate (Stepan)
PEG 4-150 mono, dioleate	Kessco® PEG 200-6000 mono, dioteate (Stepan)
PEG 4-150 mono, distearate	Kessco® 200-6000 mono, distearate (Stepan)

TABLE 84

Polyethylene Glycol Glycerol Fatty Acid Esters

Suitable PEG glycerol fatty acid esters are shown here in Table 84.

PEG Glycerol Fatty Acid Esters		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-20 glyceryl laurate	Tagat® L (Goldschmidt)	16
PEG-30 glyceryl laurate	Tagat® L2 (Goldschmidt)	16
PEG-15 glyceryl laurate	Glycerox L series (Croda)	15
PEG-40 glyceryl laurate	Glycerox L series (Croda)	15
PEG-20 glyceryl stearate	Capmul® EMG (ABITEC), Aldo® MS-20 KFG (Lonza)	13
PEG-20 glyceryl oleate	Tagat® O (Goldschmidt)	>10
PEG-30 glyceryl oleate	Tagat® O2 (Goldschmidt)	>10

TABLE 85

Alcohol--Oil Transesterification Products

A large number of 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. In certain embodiments, the oils used are castor oil or hydrogenated castor oil or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond oil. Examples of alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, sorbitol, and pentaerythritol. Representative surfactants of this class suitable for use in the present invention are shown here in Table 85.

Transesterification Products of Oils and Alcohols		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-3 castor oil	Nikkol CO-3 (Nikko)	3
PEG-5, 9, and 16 castor oil	ACCONON CA series (ABITEC)	6-7
PEG-20 castor oil	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
PEG-23 castor oil	Emulgante EL23	>10
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion), Alkamuls® EL 620 (Rhone- Poulenc), Incrocas 30 (Croda)	11
PEG-35 castor oil	Cremophor EL and EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 castor oil	Emulgante EL 65 (Condea)	
PEG-40 castor oil	Emalex C-40 (Nihon Emulsion), Alkamuls® EL 719 (Rhone- Poulenc)	13
PEG-50 castor oil	Emalex C-50 (Nihon Emulsion)	14
PEG-56 castor oil	Eumulgin® PRT 56 (Pulcra SA)	>10
PEG-60 castor oil	Nikkol CO-60TX (Nikko)	14
PEG-100 castor oil	Thornley	>10
PEG-200 castor oil	Eumulgin® PRT 200 (Pulcra SA)	>10
PEG-5 hydrogenated castor oil	Nikkol HCO-5 (Nikko)	6
PEG-7 hydrogenated castor oil	Simusol® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 hydrogenated castor oil	Nikkol HCO-10 (Nikko)	6.5
PEG-20 hydrogenated castor oil	Nikkol HCO-20 (Nikko)	11

Transesterification Products of Oils and Alcohols		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-25 hydrogenated castor oil	Simulsol® 1292 (Seppic), Cerex ELS 250 (Auschem SpA)	11
PEG-30 hydrogenated castor oil	Nikkol HCO-30 (Nikko)	11
PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
PEG-45 hydrogenated castor oil	Cerex ELS 450 (Auschem Spa)	14
PEG-50 hydrogenated castor oil	Emalex HC-50 (Nihon Emulsion)	14
PEG-60 hydrogenated castor oil	Nikkol HCO-60 (Nikko), Cremophor RH 60 (BASF)	15
PEG-80 hydrogenated castor oil	Nikkol HCO-80 (Nikko)	15
PEG-100 hydrogenated castor oil	Nikkol HCO-100 (Nikko)	17
PEG-6 corn oil	Labrafil® M 2125 CS (Gattefosse)	4
PEG-6 almond oil	Labrafil® M 1966 CS (Gattefosse)	4
PEG-6 apricot kernel oil	Labrafil® M 1944 CS (Gattefosse)	4
PEG-6 olive oil	Labrafil® M 1980 CS (Gattefosse)	4
PEG-6 peanut oil	Labrafil® M 1969 CS (Gattefosse)	4
PEG-6 hydrogenated palm kernel oil	Labrafil® M 2130 BS (Gattefosse)	4
PEG-6 palm kernel oil	Labrafil® M 2130 CS (Gattefosse)	4
PEG-6 triolein	Labrafil® M 2735 CS (Gattefosse)	4
PEG-8 corn oil	Labrafil® WL 2609 BS (Gattefosse)	6-7
PEG-20 corn glycerides	Crovol M40 (Croda)	10
PEG-20 almond glycerides	Crovol A40 (Croda)	10
PEG-25 trioleate	TAGAT® TO (Goldschmidt)	11
PEG-40 palm kernel oil	Crovol PK-70	>10
PEG-60 corn glycerides	Crovol M70(Croda)	15
PEG-60 almond glycerides	Crovol A70 (Croda)	15
PEG-4 caprylic/capric triglyceride	Labrafac® Hydro (Gattefosse),	4-5
PEG-8 caprylic/capric	Labrasol (Gattefosse), Labrafac CM 10	>10

Transesterification Products of Oils and Alcohols		
Compound	**Commercial Product (Supplier)**	**HLB**
glycerides	(Gattefosse)	
PEG-6 caprylic/capric glycerides	SOFTIGEN® 767 (Huls), Glycerox 767 (Croda)	19
Lauroyl macrogol-32 glyceride	GELUCIRE 44/14 (Gattefosse)	14
Stearoyl macrogol glyceride	GELUCIRE 50/13 (Gattefosse)	13
Mono, di, tri, tetra esters of vegetable oils and sorbitol	SorbitoGlyceride (Gattefosse)	<10
Pentaerythrityl tetraisostearate	Crodamol PTIS (Croda)	<10
Pentaerythrityl distearate	Albunol DS (Taiwan Surf.)	<10
Pentaerythrityl tetraoleate	Liponate PO-4 (Lipo Chem.)	<10
Pentaerythrityl tetrastearate	Liponate PS-4 (Lipo Chem.)	<10
Pentaerythrityl tetracaprylate/ tetracaprate	Liponate PE-810 (Lipo Chem.), Crodamol PTC (Croda)	<10
Pentaerythrityl tetraoctanoate	Nikkol Pentarate 408 (Nikko)	

TABLE 86

Polyglycerized Fatty Acids

Polyglycerol esters of fatty acids are also suitable surfactants for the present invention. Examples of suitable polyglyceryl esters are shown here in Table 86.

Polyglycerized Fatty Acids		
Compound	**Commercial Product (Supplier)**	**HLB**
Polyglyceryl-2 stearate	Nikkol DGMS (Nikko)	5-7
Polyglyceryl-2 oleate	Nikkol DGMO (Nikko)	5-7
Polyglyceryl-2 isostearate	Nikkol DGMIS (Nikko)	5-7
Polyglyceryl-3 oleate	Caprol® 3G0 (ABITEC), Drewpol 3-1-O (Stepan)	6.5
Polyglyceryl-4 oleate	Nikkol Tetraglyn 1-O (Nikko)	5-7
Polyglyceryl-4 stearate	Nikkol Tetraglyn 1-S (Nikko)	5-6
Polyglyceryl-6 oleate	Drewpol 6-1-O (Stepan), Nikkol Hexaglyn 1-O (Nikko)	9
Polyglyceryl-10 laurate	Nikkol Decaglyn 1-L (Nikko)	15
Polyglyceryl-10 oleate	Nikkol Decaglyn 1-O (Nikko)	14
Polyglyceryl-10 stearate	Nikkol Decaglyn 1-S (Nikko)	12
Polyglyceryl-6 ricinoleate	Nikkol Hexaglyn PR-15 (Nikko)	
Polyglyceryl-10 linoleate	Nikkol Decaglyn I-LN (Nikko)	12
Polyglyceryl-6 pentaoleate	Nikkol Hexaglyn S-O (Nikko)	<10
Polyglyceryl-3 dioleate	Cremophor G032 (BASF)	<10
Polyglyceryl-3 distearate	Cremophor GS32 (BASF)	<10
Polyglyceryl-4 pentaoleate	Nikkol Tetraglyn 5-O (Nikko)	<10
Polyglyceryl-6 dioleate	Caprol® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8.5
Polyglyceryl-2 dioleate	Nikkol DGDO (Nikko)	7
Polyglyceryl-10 trioleate	Nikkol Decaglyn 3-O (Nikko)	7

Polyglycerized Fatty Acids		
Compound	**Commercial Product (Supplier)**	**HLB**
Polyglyceryl-10 pentaoleate	Nikkol Decaglyn 5-O (Nikko)	3.5
Polyglyceryl-10 septaoleate	Nikkol Decagtyn 7-O (Nikko)	3
Polyglyceryl-10 tetraoleate	Caprol® 10G40 (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6.2
Polyglyceryl-10 decaisostearate	Nikkol Decaglyn 10-IS (Nikko)	<10
Polyglyceryl-10 decaoleate	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3.5
Polyglyceryl-10 mono, dioleate	Caprol® PGE 860 (ABITEC)	11
Polyglyceryl polyricinoleate	Polymuls (Henkel)	3-20

TABLE 87

Propylene Glycol Fatty Acid Esters

Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. Examples of surfactants of this class are given here in Table 87.

Propylene Glycol Fatty Acid Esters		
Compound	**Commercial Product (Supplier)**	**HLB**
Propylene glycol monocaprylate	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
Propylene glycol monolaurate	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
Propylene glycol oleate	Lutrol OP2000 (BASF)	<10
Propylene glycol myristate	Mirpyl	<10
Propylene glycol monostearate	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo® PGHMS (Lonza)	3-4
Propylene glycol hydroxy stearate		<10
Propylene glycol ricinoleate	PROPYMULS (Henkel)	<10
Propylene glycol isostearate		<10
Propylene glycol monooleate	Myverol P-06 (Eastman)	<10
Propylene glycol dicaprylate/dicaprate	Captex® 200 (ABITEC), Miglyol® 840 (Huls), Neobee® M-20 (Stepan)	>6
Propylene glycol dioctanoate	Captex® 800 (ABITEC)	
Propylene glycol caprylate/caprate	LABRAFAC PG (Gattefosse)	>6
Propylene glycol dilaurate		>6
Propylene glycol distearate	Kessco® PGDS (Stepan)	>6
Propylene glycol dicaprylate	Nikkol Sefsol 228 (Nikko)	>6
Propylene glycol dicaprate	Nikkol PDD (Nikko)	>6

TABLE 88

Mixtures of Propylene Glycol Esters--Glycerol Esters

In general, mixtures of surfactants are also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters are suitable and are commercially available. Examples of these surfactants are shown here in Table 88.

Glycerol/Propylene Glycol Fatty Acid Esters		
Compound	**Commercial Product (Supplier)**	**HLB**
Oleic	ATMOS 300, ARLACEL 186 (ICI)	3-4
Stearic	ATMOS 150	3-4

TABLE 89

Mono- and Diglycerides

Another class of surfactants is the class of mono- and diglycerides. These surfactants are generally lipophilic. Examples of these surfactants are given here in Table 89.

Mono- and Diglyceride Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
Monopalmitolein (C16:1)	(Larodan)	<10
Monoelaidin (C18:1)	(Larodan)	<10
Monocaproin (C6)	(Larodan)	<10
Monocaprylin	(Larodan)	<10
Monocaprin	(Larodan)	<10
Monolaurin	(Larodan)	<10
Glyceryl monomyristate (C14)	Nikkol MGM (Nikko)	3-4
Glyceryl monooleate (C18:1)	PECEOL (Gattefosse), Hodag GMO-D, Nikkol MGO (Nikko)	3-4
Glyceryl monooleate	RYLO series (Danisco), DIMODAN series (Danisco), EMULDAN (Danisco), ALDO® MO FG (Lonza), Kessco GMO (Stepan), MONOMULS® series (Henkel), TEGIN O, DREWMULSE GMO (Stepan), Atlas G-695 (ICI), GMOrphic 80 (Eastman), ADM DMG-40, 70, and 100 (ADM), Myverol (Eastman)	3-4
Glycerol monooleate/ linoleate	OLICINE (Gattefosse)	3-4
Glycerol monolinoleate	Maisine (Gattefosse), MYVEROL 18-92, Myverol 18-06 (Eastman)	3-4
Glyceryl ricinoleate	Softigen® 701 (Huls), HODAG GMR-D (Calgene), ALDO® MR (Lonza)	6
Glyceryl monolaurate	ALDO® MLD (Lonza), Hodag GML (Calgene)	6.8
Glycerol monopalmitate	Emalex GMS-P (Nihon)	4
Glycerol monostearate	Capmul® GMS. (ABITEC), Myvaplex (Eastman), IMWITOR® 191 (Huls), CUTINA GMS, Aldo® MS (Lonza), Nikkol MGS series (Nikko)	5-9
Glyceryl mono-, dioleate	Capmul® GMO-K (ABITEC)	<10

Mono- and Diglyceride Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
Glyceryl palmitic/stearic	CUTINA MD-A, ESTAGEL-G18	<10
Glyceryl acetate	Lamegin® EE (Grunau GmbH)	<10
Glyceryl laurate	Inwitor® 312 (Huls), Monomuls® 90-45 (Grunau GmbH), Aldo® MLD (Lonza)	4
Glyceryl citrate/ lactate/oleate/ linoieate	Imwitor® 375 (Huls)	<10
Glyceryl caprylate	Imwitor® 308 (Huls), Capmul® MCMC8 (ABITEC)	5-6
Glyceryl caprylate/caprate	Capmul® MCM (ABITEC)	5-6
Caprylic acid mono, diglycerides	Imwitor® 988 (Huls)	5-6
Caprylic/capric glycerides	Imwitor® 742 (Huls)	<10
Mono-and diacetylated monoglycerides	Myvacet® 9-45, Myvacet® 9-40, Myvacet® 9-08 (Eastman), Lamegin® (Grunau)	3.8-4
Glyceryl monostearate	Aldo® MS, Arlacel 129 (ICI), LIPO GMS (Lipo Chem.), Imwitor® 191 (Huls), Myvaplex (Eastman)	4.4
Lactic acid esters of mono, diglycerides	LAMEGIN GLP (Henkel)	<10
Dicaproin (C6)	(Larodan)	<10
Dicaprin (C10)	(Larodan)	<10
Dioctanoin (C8)	(Larodan)	<10
Dimyristin (C14)	(Larodan)	<10
Dipalmitin (C16)	(Larodan)	
Distearin	(Larodan)	<10
Glyceryl dilaurate (C12)	Capmul® GDL (ABITEC)	3-4
Glyceryl dioleate	Capmul® GDO (ABITEC)	3-4
Glycerol esters of fatty acids	GELUCIRE 39/01 (Gattefosse), GELUCIRE 43/01 (Gattefosse) GELUCIRE 37/06 (Gattefosse)	1 6
Dipalmitolein (C16:1) 1, 2 and 1,3-diolein (C18:1)	(Larodan)	<10
Dielaidin (C18:1)	(Larodan)	<10
Dilinolein (C18:2)	(Larodan)	<10

TABLE 90

Sterol and Sterol Derivatives

Sterols and derivatives of sterols are suitable surfactants for use in the present invention. These surfactants can be hydrophilic or lipophilic. Examples of surfactants of this class are shown here in Table 90.

Sterol and Sterol Derivative Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
Cholesterol, sitosterol, lanosterol		<10
PEG-24 cholesterol ether	Solulan C-24 (Amerchol)	>10
PEG-30 cholestanol	Nikkol DHC (Nikko)	>10
Phytosterol	GENEROL series (Henkel)	<10
PEG-25 phyto sterol	Nikkol BPSH-25 (Nikko)	>10
PEG-5 soya sterol	Nikkol BPS-S (Nikko)	<10
PEG-10 soya sterol	Nikkol BPS-10 (Nikko)	<10
PEG-20 soya sterol	Nikkol BPS-20 (Nikko)	<10
PEG-30 soya sterol	Nikkol BPS-30 (Nikko)	>10

TABLE 91

Polyethylene Glycol Sorbitan Fatty Acid Esters

A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in the present invention. In general, these surfactants are hydrophilic, although several lipophilic surfactants of this class can be used. Examples of these surfactants are shown here in Table 91.

PEG-Sorbitan Fatty Acid Esters		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-10 sorbitan laurate	Liposorb L-10 (Lipo Chem.)	>10
PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-4 sorbitan monolaurate	Tween-21 (Atlas/ICI), Crillet 11 (Croda)	13
PEG-80 sorbitan monolaurate	Hodag PSML-80 (Calgene); T-Maz 28	>10
PEG-6 sorbitan monolaurate	Nikkol GL-1 (Nikko)	16
PEG-20 sorbitan monopalmitate	Tween-40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-4 sorbitan monostearate	Tween-61 (Atlas/ICI), Crillet 31 (Croda)	9.6
PEG-8 sorbitan monostearate	DACOL MSS (Condea)	>10
PBG-6 sorbitan monostearate	Nikkol TS106 (Nikko)	11
PEG-20 sorbitan tristearate	Tween-65 (Atlas/ICI), Crillet 35 (Croda)	11
PEG-6 sorbitan tetrastearate	Nikkol GS-6 (Nikko)	3
PEG-60 sorbitan tetrastearate	Nikkol GS-460 (Nikko)	13
PEG-5 sorbitan monooleate	Tween-81 (Atlas/ICI), Crillet 41 (Croda)	10
PEG-6 sorbitan monooleate	Nikkol TO-106 (Nikko)	10
PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15

PEG-Sorbitan Fatty Acid Esters		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-40 sorbitan oleate	Emalex ET 8040, (Nihon Emulsion)	18
PEG-20 sorbitan trioleate	Tween-85 (Atlas/ICI), Crillet 45 (Croda)	11
PEG-6 sorbitan tetraoleate	Nikkol GO-4 (Nikko)	8.5
PEG-30 sorbitan tetraoleate	Nikkol GO-430 (Nikko)	12
PEG-40 sorbitan tetraoleate	Nikkol GO-440 (Nikko)	13
PEG-20 sorbitan monoisostearate	Tween-120 (Atlas/ICI), Crillet 6 (Croda)	>10
PEG sorbitol hexaoleate	Atlas G-1086 (ICI)	10
PEG-6 sorbitol hexastearate	Nikkol GS-6 (Nikko)	3

TABLE 92

Polyethylene Glycol Alkyl Ethers

Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in the present invention. Examples of these surfactants are shown here in Table 92.

Polyethylene Glycol Alkyl Ethers		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-2 oleyl ether, oleth-2	Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether, oleth-3	Volpo 3 (Croda)	<10
PEG-5 oleyl ether, oleth-5	Volpo 5 (Croda)	<10
PEG-10 oleyl ether, oleth-10	Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether, oleth-20	Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauryl ether, laureth-4	Brij 30 (Atlas/ICI)	9.7
PEG-9 lauryl ether		>10
PEG-23 lauryl ether, laureth-23	Brij 35 (Atlas/ICI)	17
PEG-2 cetyl ether	Brij 52 (ICI)	5.3
PEG-10 cetyl ether	Brij 56 (ICI)	13
PEG-20 cetyl ether	Brij 58 (ICI)	16
PEG-2 stearyl ether	Brij 72 (ICI)	4.9
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-20 stearyl ether	Brij 78 (ICI)	15
PEG-100 stearyl ether	Brij 700 (ICI)	>10

TABLE 93

Sugar Esters

Esters of sugars are suitable surfactants for use in the present invention. Examples of such surfactants are shown here in Table 93.

Sugar Ester Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
Sucrose distearate	SUCRO ESTER 7 (Gattefosse), Crodesta F-10 (Croda)	3
Sucrose distearate/ monostearate	SUCRO ESTER 11 (Gattefosse), Crodesta F-110 (Croda)	12
Sucrose dipalmitate		7.4
Sucrose monostearate	Crodesta F-160 (Croda)	15
Sucrose monopalmitate	SUCRO ESTER 15 (Gattefosse)	>10
Sucrose monolaurate	Saccharose monolaurate 1695 (Mitsubishi-Kasei)	15

TABLE 94

Polyethylene Glycol Alkyl Phenols

Several hydrophilic PEG-alkyl phenol surfactants are available, and are suitable for use in the present invention. Examples of these surfactants are shown here in Table 94.

Polyethylene Glycol Alkyl Phenol Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
PEG-10-100 nonyl phenol	Triton X series (Rohm & Haas), Igepal CA series (GAF, USA), Antarox CA series (GAF, UK)	>10
PEG-15-100 octyl phenol ether	Triton N-series (Rohm & Haas), Igepal CO series (GAF, USA), Antarox CO series (GAF, UK)	>10

TABLE 95

Polyoxyethylene-Polyoxypropylene Block Copolymers

The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and lipophilic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in the present invention. These surfactants are available under various trade names, including Synperonic PE series (ICI); Pluronic® series (BASF), Emkalyx, Lutrol (BASF), Supronic, Monolan, Pluracare, and Plurodac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.

Examples of suitable surfactants of this class are shown here in Table 95. Since the compounds are widely available, commercial sources are not listed in the Table. The compounds are listed by generic name, with the corresponding "a" and "b" values.

POE-POP Block Copolymers			
Compound	**a, b values in $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$**		**HLB**
Poloxamer 105	a = 11	b = 16	8
Poloxamer 108	a = 46	b = 16	>10
Poloxamer 122	a = 5	b = 21	3
Poloxamer 123	a = 7	b = 21	7
Poloxamer 124	a = 11	b = 21	>7
Poloxamer 181	a = 3	b = 30	
Poloxamer 182	a = 8	b = 30	2
Poloxamer 183	a = 10	b = 30	
Poloxamer 184	a = 13	b = 30	
Poloxamer 185	a = 19	b = 30	

POE-POP Block Copolymers			
Compound	a, b values in $HO(C_2H_4O)_a (C_3H_6O)_b (C_2H_4O)_aH$		HLB
Poloxamer 188	a = 75	b = 30	29
Poloxamer 212	a = 8	b = 35	
Poloxamer 215	a = 24	b = 35	
Poloxamer 217	a = 52	b = 35	
Poloxamer 231	a = 16	b = 39	
Poloxamer 234	a = 22	b = 39	
Poloxamer 235	a = 27	b = 39	
Poloxamer 237	a = 62	b = 39	24
Poloxamer 238	a = 97	b = 39	
Poloxamer 282	a = 10	b = 47	
Poloxamer 284	a = 21	b = 47	
Poloxamer 288	a = 122	b = 47	>10
Poloxamer 331	a = 7	b = 54	0.5
Poloxamer 333	a = 20	b = 54	
Poloxamer 334	a = 31	b = 54	
Poloxamer 335	a = 38	b = 54	
Poloxamer 338	a = 128	b = 54	
Poloxamer 401	a = 6	b = 67	
Poloxamer 402	a = 13	b = 67	
Poloxamer 403	a = 21	b = 67	
Poloxamer 407	a = 98	b = 67	

TABLE 96

Sorbitan Fatty Acid Esters

Sorbitan esters of fatty acids are suitable surfactants for use in the present invention.

Examples of these surfactants are shown here in Table 96.

Sorbitan Fatty Acid Ester Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7
Sorbitan trioleate	Span-85 (Atlas/ICI), Crill 45 (Croda), Nikkol SO-30 (Nikko)	4.3
Sorbitan sesquioleate	Arlacel-C (ICI), Crill 43 (Croda), Nikkol SO-15 (Nikko)	3.7
Sorbitan tristearate	Span-65 (Atlas/ICI) Crill 35 (Croda), Nikkol SS-30 (Nikko)	2.1
Sorbitan monoisostearate	Crill 6 (Croda), Nikkol SI-10 (Nikko)	4.7
Sorbitan sesquistearate	Nikkol SS-15 (Nikko)	4.2

TABLE 97

Lower Alcohol Fatty Acid Esters

Esters of lower alcohols (C_2 to C_4) and fatty acids (C_8 to C_{18}) are suitable surfactants for use in the present invention. Examples of these surfactants are shown here in Table 97.

Lower Alcohol Fatty Acid Ester Surfactants		
Compound	**Commercial Product (Supplier)**	**HLB**
Ethyl oleate	Crodamol EO (Croda), Nikkol EOO (Nikko)	<10
Isopropyl myristate	Crodamol IPM (Croda)	<10
Isopropyl palmitate	Crodamol IPP (Croda)	<10
Ethyl linoleate	Nikkol VF-E (Nikko)	<10
Isopropyl linoleate	Nikkol VF-IP (Nikko)	<10

TABLE 98

Ionic Surfactants

Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in the present invention. Preferred anionic surfactants include fatty acid salts and bile salts. Preferred cationic surfactants include carnitines. Specifically, preferred ionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate; lauroyl carnitine; palmitoyl carnitine; and myristoyl carnitine. Examples of such surfactants are shown here in Table 98. For simplicity, typical counterions are shown in the entries in the Table. It will be appreciated by one skilled in the art, however, that any bioacceptable counterion can be used. For example, although the fatty acids are shown as sodium salts, other cation counterions can also be used, such as alkali metal cations or ammonium. Unlike typical non-ionic surfactants, these ionic surfactants are generally available as pure compounds, rather than commercial (proprietary) mixtures. Because these compounds are readily available from a variety of commercial suppliers, such as Aldrich, Sigma, and the like, commercial sources are not generally listed in the Table.

Ionic Surfactants	
Compound	**HLB**
FATTY ACID SALTS	>10
Sodium caproate	
Sodium caprylate	
Sodium caprate	
Sodium laurate	
Sodium myristate	
Sodium myristolate	
Sodium palmitate	
Sodium palmitoleate	
Sodium oleate	18

Ionic Surfactants	
Compound	**HLB**
Sodium ricinoleate	
Sodium linoleate	
Sodium linolenate	
Sodium stearate	
Sodium lauryl sulfate (dodecyl)	40
Sodium tetradecyl sulfate	
Sodium lauryl sarcosinate	
Sodium dioctyl sulfosuccinate [sodium docusate (Cytec)]	
BILE SALTS	>10
Sodium cholate	
Sodium taurocholate	
Sodium glycocholate	
Sodium deoxycholate	
Sodium taurodeoxycholate	
Sodium glycodeoxycholate	
Sodium ursodeoxycholate	
Sodium chenodeoxycholate	
Sodium taurochenodeoxycholate	
Sodium glycol cheno deoxycholate	
Sodium cholylsarcosinate	
Sodium N-methyl taurocholate	
Sodium lithocholate	
PHOSPHOLIPIDS	
Egg/Soy lecithin [Epikuron™ (Lucas Meyer), Ovothin™ (Lucas Meyer)]	
Lyso egg/soy lecithin	
Hydroxylated lecithin	
Lysophosphatidylcholine	
Cardiolipin	

Ionic Surfactants	
Compound	**HLB**
Sphingomyelin	
Phosphatidylcholine	
Phosphatidyl ethanolamine	
Phosphatidic acid	
Phosphatidyl glycerol	
Phosphatidyl serine	
PHOSPHORIC ACID ESTERS	
Diethanolammonium polyoxyethylene-10 oleyl ether phosphate	
Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride	
CARBOXYLATES	
Ether carboxylates (by oxidation of terminal OH group of fatty alcohol ethoxylates)	
Succinylated monoglycerides [LAMEGIN ZE (Henkel)]	
Sodium stearyl fumarate	
Stearoyl propylene glycol hydrogen succinate	
Mono/diacetylated tartaric acid esters of mono- and diglycerides	
Citric acid esters of mono-, diglycerides	
Glyceryl-lacto esters of fatty acids (CFR ref. 172.852)	
Acyl lactylates: lactylic esters of fatty acids calcium/sodium stearoyl-2-lactylate calcium/sodium stearoyl lactylate	
Alginate salts	
Propylene glycol alginate	
SULFATES AND SULFONATES	
Ethoxylated alkyl sulfates	
Alkyl benzene sulfones	
α-olefin sulfonates	

Ionic Surfactants	
Compound	**HLB**
Acyl isethionates	
Acyl taurates	
Alkyl glyceryl ether sulfonates	
Octyl sulfosuccinate disodium	
Disodium undecylenamideo-MEA-sulfosuccinate	
CATIONIC Surfactants	>10
Lauroyl carnitine	
Palmitoyl carnitine	
Myristoyl carnitine	
Hexadecyl triammonium bromide	
Decyl trimethyl ammonium bromide	
Cetyl trimethyl ammonium bromide	
Dodecyl ammonium chloride	
Alkyl benzyldimethylammonium salts	
Diisobutyl phenoxyethoxydimethyl benzylammonium salts	
Alkylpyridinium salts	
Betaines (trialkylglycine):	
Lauryl betaine (N-lauryl,N,N-dimethylglycine)	
Ethoxylated amines:	
Polyoxyethylene-15 coconut amine	

TABLE 99

BUPROPION HBr XL TABLETS, 348 mg
TABLET COMPOSITION (mg / tablet)

Table 1: Core Tablets

Item #	*Material*	*Qty. Required (kg)*	*% of Tablet Tablet Core Formulation*	*348 mg Strength Target Weight: 371.2mg / tablet*
RS0009	*Polyvinyl Alcohol*	*2.25 kg dispensed 2.00kg used*	*3.125%*	*11.6mg/tablet*
RA0057	*Bupropion HBr*	*60.00*	*93.750%*	*348mg/tablet*
RE0200	*Glyceryl Behenate, NF*	*2.00*	*3.125%*	*11.6mg/tablet*
RS0003	**Purified Water, USP*	*47.75*	*0*	*0*
Theoretical Batch Size: kg		*64.00*	*100%*	*371.2mg/tablet*

*Evaporated during granulating process and not included in tablet core composition.

TABLE 100.

Table 2: Coated / Printed Tablets

348 mg XL Coated / Printed Tablets – Pivotal Coating Formulation / Batch Size				
Item #	Material	Qty. Required (kg)	% of Batch	Applied Solids Mg / tablet Target Weight Gain: 32 mg (Range: 30 – 34mg/tablet)
RE0233	Ethylcellulose 100, NF	3.230	4.61%	16.406 mg
RE0067	Povidone, USP	2.000	2.86%	10.159 mg
RE0331	Polyethylene Glycol 4000, NF	0.720	1.03%	3.657 mg
RE0103	Dibutyl Sebacate, NF	0.350	0.50%	1.778 mg
*RS0010	*Dehydrated Alcohol, 200 proof, USP	57.300	81.86%	0
*RS0006	*Ethyl Alcohol, 95%, USP	6.400	9.14%	0
COATING SOLUTION TOTAL (kg)		70 kg	100%	32 mg / tablet
**RE0223	**Carnauba Wax, NF	0.010 kg	N/A	Trance Amounts
RE0234	Opacode Black Ink S-1-8090 or S-1-17823	1.00	50%	Trace Amounts to brand tablets with logo on one side BR 348
***RS0001	***Isopropyl Alcohol	1.00	50%	Used for cleaning design and transfer rolls only

Note: Where applicable, percentages and mg/tablet totals have been rounded to two decimal places. *Evaporated during coating process. **Carnauba Wax not included as part of coating solution formulation, trace amounts applied after completion of the coating process. *** Isopropyl Alcohol used for cleaning only. Only trace amounts of black ink to brand tablets with specific logo is applied to one side of tablet. Weight of this material applied to tablet cannot be measured.

TABLE 101

Table 3: BUPROPION HBr XL TABLETS, 348 mg: OVERALL FINAL PRINTED TABLET COMPOSITION / WEIGHT

Material	*348 mg (+32 mg Coating) / Overall % of Final Tablet Composition*
Polyvinyl Alcohol	11.6 mg (2.88%)
Bupropion HBr (API)	348 mg (86.29%)
Purified Water, USP	0
Glyceryl Behenate, NF	11.6 mg (2.88%)
Ethylcellulose 100, NF	16.406 mg (4.07%)
Povidone, USP	10.159 mg (2.52%)
Polyethylene Glycol 4000, NF	3.657 mg (0.91%)
Dibutyl Sebacate, NF	1.778 mg (0.44%)
Dehydrated Alcohol, 200 proof, USP	0
Ethyl Alcohol, 95%, USP	0
Carnauba Wax, NF	0.058 mg/tablet (0.01%) (based on 172,413 tablets for coating pan-load)
Opacode Black Ink S-1-8090 or S-1-17823	Trace Amounts
Isopropyl Alcohol	0
Final Printed Tablet Weight (mg)	*403.258 mg/tablet (100%)*

NOTE: Bupropion HBr XL Tablets, 174 mg and 348 mg have the same tablet core formulation and coating formulation (composition). The only difference in percentage of material per tablet is due to the differences in core tablet weight and coating weight gain. Total quantity of Carnauba Wax applied to tablets will vary based on coating pan-load. The percent (%) Composition of each ingredient in final tablet formulation, is based on final target coating weight gain and target amount of Carnauba Wax for calculation.

TABLE 102

BUPROPION HBr XL TABLETS, 174 mg
TABLET COMPOSITION (mg / tablet)

Table 1: Core Tablets

Item #	*Material*	*Qty. Required (kg)*	*% of Tablet Tablet Core Formulation*	*174 mg Strength Target Weight: 185.6 mg / tablet*
RS0009	*Polyvinyl Alcohol*	*2.25 kg dispensed 2.00kg used*	*3.125%*	*5.8 mg/tablet*
RA0057	*Bupropion HBr*	*60.00*	*93.750%*	*174 mg/tablet*
RE0200	*Glyceryl Behenate, NF*	*2.00*	*3.125%*	*5.8 mg/tablet*
RS0003	**Purified Water, USP*	*47.75*	*0*	*0*
Theoretical Batch Size: kg		*64.00*	*100%*	*185.6 mg/tablet*

*Evaporated during granulating process and not included in tablet core composition.

TABLE 103

Table 2: Coated / Printed Tablets

174 mg XL Coated / Printed Tablets – Pivotal Coating Formulation / Batch Size				
Item #	Material	Qty. Required (kg)	% of Batch	Applied Solids Mg / tablet Target Weight Gain: 30 mg (Range: 28 – 32 mg/tablet)
RE0233	Ethylcellulose 100, NF	3.230	4.61%	15.381 mg
RE0067	Povidone, USP	2.000	2.86%	9.524 mg
RE0331	Polyethylene Glycol 4000, NF	0.720	1.03%	3.428 mg
RE0103	Dibutyl Sebacate, NF	0.350	0.50%	1.667 mg
*RS0010	*Dehydrated Alcohol, 200 proof, USP	57.300	81.86%	0
*RS0006	*Ethyl Alcohol, 95%, USP	6.400	9.14%	0
COATING SOLUTION TOTAL (kg)		70 kg	100%	30 mg / tablet
**RE0223	**Carnauba Wax, NF	0.010 kg	N/A	Trance Amounts
RE0234	Opecode Black Ink S-1-8090 or S-1-17823	1.00	50%	Trace Amounts to brand tablets with logo on one side BR 174
***RS0001	***Isopropyl Alcohol	1.00	50%	Used for cleaning design and transfer rolls only

Note: Where applicable, percentages and mg/tablet totals have been rounded to two decimal places. *Evaporated during coating process. **Carnauba Wax not included as part of coating solution formulation, trace amounts applied after completion of the coating process. *** Isopropyl Alcohol used for cleaning only. Only trace amounts of black ink to brand tablets with specific logo is applied to one side of tablet. Weight of this material applied to tablet cannot be measured.

TABLE 104

Table 3: BUPROPION HBr XL TABLETS, 174 mg: OVERALL FINAL PRINTED TABLET COMPOSITION / WEIGHT

Material	*174 mg (+30 mg Coating) / Overall % of Final Tablet Composition*
Polyvinyl Alcohol	5.8 mg (2.69%)
Bupropion HBr (API)	174 mg (80.68%)
Purified Water, USP	0
Glyceryl Behenate, NF	5.8 mg (2.69%)
Ethylcellulose 100, NF	15.381 mg (7.13%)
Povidone, USP	9.524 mg (4.42%)
Polyethylene Glycol 4000, NF	3.428 mg (1.59%)
Dibutyl Sebacate, NF	1.667 mg (0.77%)
Dehydrated Alcohol, 200 proof, USP	0
Ethyl Alcohol, 95%, USP	0
Carnauba Wax, NF	0.058 mg/tablet (0.03%) (based on 172,413 tablets for coating pan-load)
Opaicode Black Ink S-1-8090 or S-1-17823	Trace Amounts
Isopropyl Alcohol	0
Final Printed Tablet Weight (mg)	*215.658 mg/tablet (100%)*

NOTE: Bupropion HBr XL Tablets, 174 mg and 348 mg have the same tablet core formulation and coating formulation (composition). The only difference in percentage of material per tablet is due to the differences in core tablet weight and coating weight gain. Total quantity of Carnauba Wax applied to tablets will vary based on coating pan-load. The percent (%) Composition of each ingredient in final tablet formulation, is based on final target coating weight gain and target amount of Carnauba Wax for calculation.

TABLE 105(1)

ACCELERATED STABILITY

ACCELERATED STABILITY PROGRAM				
Product: Bupropion.HBr FV0092	Batch No.: D00894	Start date: 20/12/04	Temperature: 40°C ± 2°C R.H.: 75% ± 5%	
Analysis	**Specification**	**time 0**	**3 month**	**6 months**
Description	white or almost white crystalline powder	conform	conform	conform
Identification	IR, HPLC (positive)	positive	positive	positive
Water content (K.F.)	NMT 0.5 %	0.05	0.07	0.08
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.	1) 0.05
	2) NMT 0.1%	2) n.d.	2) n.d.	2) n.d.
	3) NMT 0.1%	3) n.q.	3) n.q.	3) n.q.
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03	4) 0.04
	5) NMT 0.1%	5) 0.04	5) 0.04	5) n.q.
	6) NMT 0.3%	6) 0.04	6) 0.06	6) 0.02
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1
Assay (HPLC)	98.0 - 102.0 % on d.b.	99.6	99.6	99.7

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).
Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Bupropion.HBr Stability Data

TABLE 105(2)

ACCELERATED STABILITY PROGRAM				
Product: Bupropion.HBr FV0092	Batch No.: D00895	Start date: 20/12/04		Temperature: 40°C ± 2°C R.H.: 75% ± 5%
Analysis	**Specification**	**time 0**	**3 month**	**6 months**
Description	white or almost white crystalline powder	conform	conform	conform
Identification	IR, HPLC (positive)	positive	positive	positive
Water content (K.F.)	NMT 0.5 %	0.04	0.07	0.07
Chromatographic purity A) (HPLC)	1) NMT 0.1% 2) NMT 0.1% 3) NMT 0.1%	1) n.d. 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) 0.05	1) 0.05 2) n.d. 3) n.q.
Chromatographic purity B) (HPLC)	4) NMT 0.1% 5) NMT 0.1% 6) NMT 0.3%	4) 0.04 5) 0.04 6) 0.04	4) 0.03 5) 0.04 6) 0.05	4) 0.04 5) n.q. 6) 0.02
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1
Assay (HPLC)	98.0 - 102.0 % on d.b.	99.2	100.7	99.7

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).

Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Bupropion.HBr Stability Data

TABLE 105(3)

ACCELERATED STABILITY PROGRAM				
Product: Bupropion.HBr FV0092	Batch No.: D00896	Start date: 20/12/04		Temperature: 40°C ± 2°C R.H.: 75% ± 5%
Analysis	Specification	time 0	3 month	6 months
Description	white or almost white crystalline powder	conform	conform	conform
Identification	IR, HPLC (positive)	positive	positive	positive
Water content (K.F.)	NMT 0.5 %	0.06	0.11	0.04
Chromatographic purity A) (HPLC)	1) NMT 0.1% 2) NMT 0.1% 3) NMT 0.1%	1) n.d. 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) 0.05 2) n.d. 3) n.q.
Chromatographic purity B) (HPLC)	4) NMT 0.1% 5) NMT 0.1% 6) NMT 0.3%	4) 0.04 5) 0.05 6) 0.05	4) 0.03 5) 0.04 6) 0.05	4) 0.04 5) n.q. 6) n.q.
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1
Assay (HPLC)	98.0 - 102.0 % on d.b.	99.3	100.0	100.4

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).

Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Bupropion.HBr Stability Data

TABLE 105(4)

SHELF LIFE

SHELF LIFE STABILITY PROGRAM									
Product: Bupropion.HBr FV0092	Batch No.: D00894		Start date: 20/12/04			Temperature: 25°C ± 2°C; Relative Humidity: 60% ± 5%			
Analysis	Specification	time 0	3 months	6 months	9 months	12 months	18 months	24 months	36 months
Description	white or almost white crystalline powder	conform	conform	conform	conform	conform			
Identification	IR, HPLC (positive)	positive	positive	positive	positive	positive			
Water content (K.F.)	NMT 0.5 %	0.05	0.05	0.06	0.05	0.05			
Chromatographic purity A) (HPLC)	1) NMT 0.1%	1) n.d.	1) n.q.	1) 0.05	1) n.q.	1) n.d.	1)	1)	1)
	2) NMT 0.1%	2) n.d.	2) n.d.	2) n.d.	2) n.d.	2) n.d.	2)	2)	2)
	3) NMT 0.1%	3) n.q.	3) n.q.	3) n.q.	3) n.q.	3) 0.05	3)	3)	3)
Chromatographic purity B) (HPLC)	4) NMT 0.1%	4) 0.04	4) 0.03	4) 0.05	4) n.d.	4) 0.05	4)	4)	4)
	5) NMT 0.1%	5) 0.04	5) 0.04	5) n.q.	5) n.q.	5) 0.05	5)	5)	5)
	6) NMT 0.3%	6) 0.04	6) 0.05	6) 0.02	6) n.q.	6) 0.07	6)	6)	6)
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	n.q.	0.2			
Assay (HPLC)	98.0 - 102.0% on d.b.	99.6	99.4	100.2	99.5	99.6			
Microbial cont.	• total microbial count < 1000 cfu/g • moulds and yeast < 100 cfu/g	not applied	not applied	not applied	not applied	< 100 ufc/g < 100 ufc/g	not applied		

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).
Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Bupropion.HBr Stability Data

TABLE 105(5)

SHELF LIFE STABILITY PROGRAM									
Product: Bupropion.HBr FV0092	Batch No.: D00895		Start date: 20/12/04			Temperature: 25°C ± 2°C; Relative Humidity: 60% ± 5%			
Analysis	**Specification**	**time 0**	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months**
Description	white or almost white crystalline powder	conform	conform	conform	conform	conform			
Identification	IR, HPLC (positive)	positive	positive	positive	positive	positive			
Water content (K.F.)	NMT 0.5 %	0.04	0.04	0.05	0.05	0.04			
Chromatographic purity A) (HPLC)	1) NMT 0.1% 2) NMT 0.1% 3) NMT 0.1%	1) n.d. 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) 0.05 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) n.d. 2) n.d. 3) 0.05	1) 2) 3)	1) 2) 3)	1) 2) 3)
Chromatographic purity B) (HPLC)	4) NMT 0.1% 5) NMT 0.1% 6) NMT 0.3%	4) 0.04 5) 0.04 6) 0.04	4) 0.03 5) 0.04 6) 0.05	4) 0.05 5) n.q. 6) 0.02	4) n.d. 5) n.q. 6) n.q.	4) 0.05 5) 0.07 6) 0.07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	n.q.	0.2			
Assay (HPLC)	98.0 - 102.0% on d.b.	99.2	99.5	100.1	99.4	99.4			
Microbial cont.	• total microbial count < 1000 cfu/g • moulds and yeast < 100 cfu/g	not applied	not applied	not applied	not applied	< 100 ufc/g < 100 ufc/g	not applied		

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).

Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Bupropion.HBr Stability Data

TABLE 105(6)

SHELF LIFE STABILITY PROGRAM									
Product: Bupropion.HBr FV0092	Batch No.: D00896		Start date: 20/12/04			Temperature: 25°C ± 2°C; Relative Humidity: 60% ± 5%			
Analysis	**Specification**	**time 0**	**3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**	**36 months**
Description	white or almost white crystalline powder	conform	conform	conform	conform	conform			
Identification	IR, HPLC (positive)	positive	positive	positive	positive	positive			
Water content (K.F.)	NMT 0.5 %	0.06	0.04	0.04	0.04	0.03			
Chromatographic purity A) (HPLC)	1) NMT 0.1% 2) NMT 0.1% 3) NMT 0.1%	1) n.d. 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) 0.05 2) n.d. 3) n.q.	1) n.q. 2) n.d. 3) n.q.	1) n.d. 2) n.d. 3) n.q.	1) 2) 3)	1) 2) 3)	1) 2) 3)
Chromatographic purity B) (HPLC)	4) NMT 0.1% 5) NMT 0.1% 6) NMT 0.3%	4) 0.04 5) 0.05 6) 0.05	4) 0.03 5) 0.04 6) 0.05	4) 0.04 5) n.q. 6) n.q.	4) n.d. 5) n.q. 6) n.q.	4) 0.05 5) 0.07 6) 0.07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Chromatographic purity (HPLC: A + B)	Total impurities NMT 0.5 %	0.1	0.1	0.1	n.q.	0.1			
Assay (HPLC)	98.0 - 102.0% on d.b.	99.3	99.4	100.5	99.4	100.3			
Microbial cont.	• total microbial count < 1000 cfu/g • moulds and yeast < 100 cfu/g	not applied	not applied	not applied	not applied	< 100 ufc/g < 100 ufc/g	not applied		

Impurities: 1) 3'-Chloropropiophenone; 2) 3'-Chloro-2-bromopropiophenone; 3) 3'-Chlorobenzoic acid ; 4) 2-N-(tert-Butyl)-aminopropiophenone; 5) single unknown impurity (each); 6) total unknown impurities (calculated from the sum of all impurity peak areas, also peaks below LOQ are included).

Notes: n.d. = not detectable; n.q. = not quantifiable; LOQ = 0.05% for imp. 1,2 and 3; LOQ = 0.02% for imp. 4 and 5; LOD = 0.01% for imp. 1 and 3; LOD = 0.04% for imp. 2; LOD = 0.002% for imp. 4 and 5.

Bupropion.HBr Stability Data

WE CLAIM:

1. A composition suitable for administration to a subject in need of treatment for a condition, comprising:

a pharmaceutically effective amount of bupropion hydrobromide salt ,

wherein said bupropion hydrobromide composition is more stable than a corresponding composition comprising bupropion hydrochloride.

2. The composition of claim 1 wherein said composition is suitable for oral administration to a subject in need of bupropion administration.

3. The composition of claim 1 wherein said bupropion hydrobromide composition is more stable than an otherwise equivalent bupropion hydrochloride composition when stored for at least 3 months at 40 degrees C and 75% relative humidity.

4. The composition of claim 3 which is more stable when stored for at least 6 months at 40 degrees C and 75% relative humidity.

5. The composition of claim 3 which contains less of at least one degradation product characteristic of bupropion degradation after being stored at 40 degrees C at 75% relative humidity than an otherwise similar bupropion hydrochloride composition stored under the same conditions.

6. The composition of claim 3 which exhibits less fluctuations in the in vitro dissolution profile in at least one dissolution media than an otherwise similar bupropion hydrochloride composition after being stored for at least 3 months at 40 degrees C and 75% relative humidity.

7. The composition of claim 1 which is coated with at least one coating which prevents dose dumping when said composition is in 40% ethanol.

8. The composition of claim 7 which comprises a SmartCoat™.

9. The composition of claim 1 which comprises at least one pharmaceutically acceptable carrier or excipient.

10. The composition of claim 1 which is in the form of a tablet that is bioequivalent to Wellbutrin™ or Zyban™/Wellbutrin™ SR tablets when administered once daily to a subject in need thereof.

11. The composition of claim 10 which does not exhibit a food effect.

12. The composition of claim 10 which comprises 150, 174, 300 or 348 mg of bupropion hydrobromide.

13. The composition of claim 1 which is suitable for administration by topical means.

14. The composition of claim 1 which is suitable for transmucosal or transdermal delivery

15. The composition of claim 1 which is suitable for injection.

16. The composition of claim 1 which is suitable for administration by an inhalation route.

17. The composition of claim 1 wherein the bupropion contained therein comprises at least 90% of one enantiomeric form of the bupropion salt.

18. The composition of claim 1 wherein the bupropion contained comprises at least 95-99% of one enantiomeric form of the bupropion salt.

19. The composition of claim 1 wherein at least 90% of the bupropion contained therein comprises the (+) enantiomer.

20. The composition of claim 1 wherein at least 90% of the bupropion contained therein comprises the (-) enantiomer.

21. The composition of claim 1 wherein at least 95-99% of the bupropion comprises the (-) enantiomer.

22. The composition of claim 1 wherein at least 95-99% of the bupropion comprises the (+) enantiomer.

23. The composition of claim 1 which comprises at least one of polymorph I, polymorph II and polymorph III.

24. The composition of claim 23 which comprises polymorphs I, II and III.

25. A substantially pure polymorph of bupropion hydrobromide.

26. The substantially pure polymorph of claim 25 which is polymorph I.

27. The substantially pure polymorph of claim 25 which is polymorph II.

28. The substantially pure polymorph of claim 25 which is polymorph III.

29. The composition of claim 1 which is in a tablet formulation.

30. The composition of claim 1 which is in a capsule formulation.

31. The composition of claim 1 wherein said composition is an extended release formulation.

32. The composition of claim 1 wherein said composition is a delayed release formulation.

33. The composition of claim 1 which is an enhanced absorption formulation.

34. The composition of claim 1 which is in a controlled release matrix tablet formulation.

35. The composition of claim 1 which is an osmotic release delivery system.

36. The composition of claim 1 which is suitable for once-daily administration.

37. The composition of claim 1 which is suitable for twice-daily administration.

38. The composition of claim 28 which is bioequivalent to Welbutrin ER or Zyban™/Wellbutrin SR when administered once daily.

39. The composition of claim 1 which comprises from 50-400 mg of bupropion.

40. The composition of claim 1 which comprises 150 or 174 mg of bupropion.

41. The composition of claim 1 which comprises 300 or 48 mg of bupropion.

42. The composition of claim 1 which comprises at least one functional or non-functional coating.

43. The composition of claim 42 wherein said coatings include moisture barriers, control-release coats, enteric coats, coatings that affect physical stability and/or coatings that affect the appearance of the composition.

44. The composition of claim 43 which comprises a moisture barrier.

45. The composition of claim 1 comprising a core that includes said bupropion salt, a binder and a lubricant; anda control releasing coat substantially

surrounding said core,wherein said composition provides controlled release of said bupropion salt.

46. The composition of claim 45 which comprises at least one additional coating.

47. The composition of claim 45 wherein said additional coatings include moisture barriers, enteric coats, control-release coats, coats that affect the physical stability of the composition and/or coatings that affect the physical appearance of the composition.

48. The composition of claim 47 wherein said additional coats substantially surround the core and/or the control-releasing coat.

49. The composition of claim 45 wherein said binder is polyvinyl alcohol.

50. The composition of claim 45 which comprises a moisture barrier or enteric coat surrounding the core and/or control-releasing coat.

51. The composition of claim 45 wherein said lubricant is glyceryl behenate.

52. The composition of claim 45 wherein said control releasing coat includes a water-insoluble polymer, a water-soluble polymer, and optionally a plasticizer.

53. The composition of claim 52 wherein said water-insoluble polymer is ethylcellulose.

54. The composition of claim 52 wherein said water-soluble polymer is polyvinylpyrrolidone.

55. The composition of claim 52 wherein said plasticizer if present comprises a mixture of polyethylene glycol 4000 and dibutyl sebacate.

56. The composition of claim 52 wherein said control releasing coat includes an aqueous dispersion of a neutral ester copolymer without any functional groups, a polyglycol having a melting point greater than about 55°C, and 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 of the polyglycol.

57. The composition of claim 56 which comprises at least one additional coat.

58. The composition of claim 55 wherein said core is a microparticle.

59. The composition of claim 55 wherein said core is an immediate release core.

60. The composition of claim 1 which additionally comprises a second drug.

61. The composition of claim 60 wherein said second drug is selected from an anti-depressant, vasodilator, anti-anxiety agent, anti-inflammatory, anti-pain agent, anti-migraine agent, anti-drug-abuse, alcohol-abuse or nicotine abuse agent, anti-viral agent, sleep modulating agent, anti-mimetic, appetite depressant or enhancer, and neuropsychiatric agent.

62. The composition of claim 60 wherein the second drug is an anti-depressant.

63. The composition of claim 60 wherein the second drug is immediately released upon administration.

64. The composition of claim 60 wherein the second drug does not come into contact with the first drug in the composition.

65. The composition of claim 64 wherein the bupropion and second drug are comprised in different layers, portions of the composition or different microparticles that are comprised in the composition.

66. The composition of claim 60 wherein said second drug is citalopram.

67. The composition of claim 60 wherein said second drug is escitalopram.

68. The composition of claim 60 wherein the second drug is venlafaxine.

69. A method of using a composition according to any one of claims 1-68 for treatment in a subject in need of bupropion administration.

70. The method of claim 69 wherein said condition is selected from the group consisting of depression, addiction disorder, smoking cessation, obesity, and seasonal effective disorder.

71. The method of claim 69 wherein said condition is obesity.

72. The method of claim 69 wherein the condition is obesity.

73. The method of claim 69 wherein the condition is smoking cessation.

74. The method of claim 69 wherein the condition is seasonal effective disorder.

75. A use of bupropion hydrobromide to prepare a medicament to treat conditions which benefit from administration of bupropion, wherein said medicament has greater stability than a corresponding medicament comprising bupropion hydrochloride.

76. The use of claim 75 wherein said greater stability results in said bupropion hydrobromide medicament containing less of at least one moiety characteristic of bupropion degradation than an otherwise similar bupropion hydrochloride composition

when said compositions are both stored for at least 3 months or at least 6 months at 40 degrees C and 75% relative humidity.

77. The use of claim 75 wherein said greater stability results in said bupropion hydrobromide medicament exhibiting less fluctuation in the in vitro dissolution profile in at least one dissolution medium relative to an otherwise similar bupropion hydrochloride composition after being stored for at least 3 months and/or 6 months at 40 degrees C and 75% relative humidity.

78. The use of claim 75 wherein the medicament is a tablet.

79. The use of claim 75 wherein the medicament is a capsule.

80. The use of claim 75 wherein the medicament contains a second drug.

81. The use of claim 80 wherein the second drug is citalopram.

82. The use of claim 80 wherein the second drug is escitalopram.

83. The use of claim 80 wherein the second drug is venlafaxine.

Figure 1

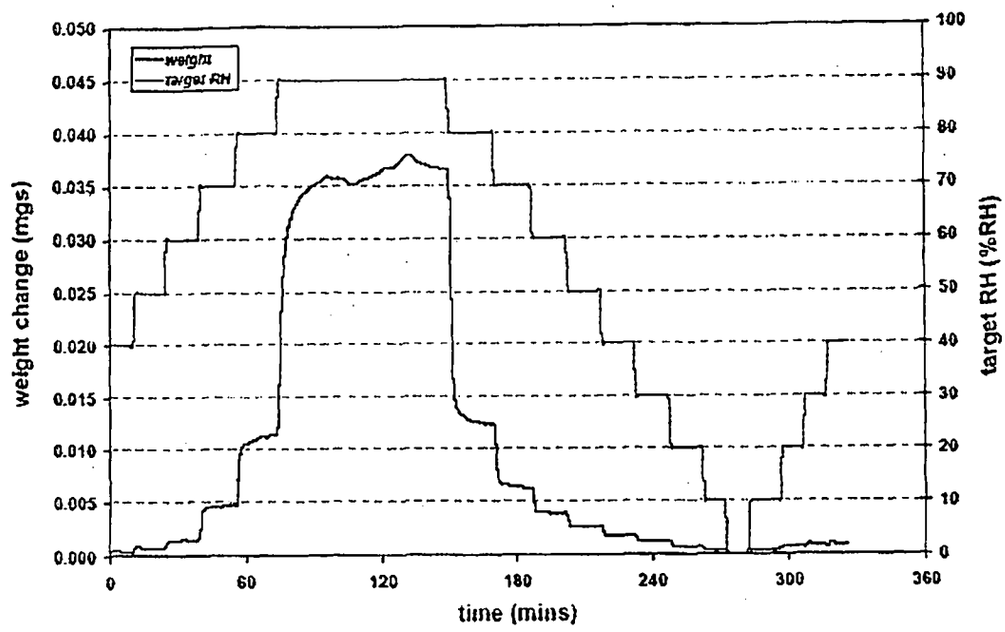

weight
target RH
weight change (mgs)
target RH (%RH)
time (mins)
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360

Figure 2

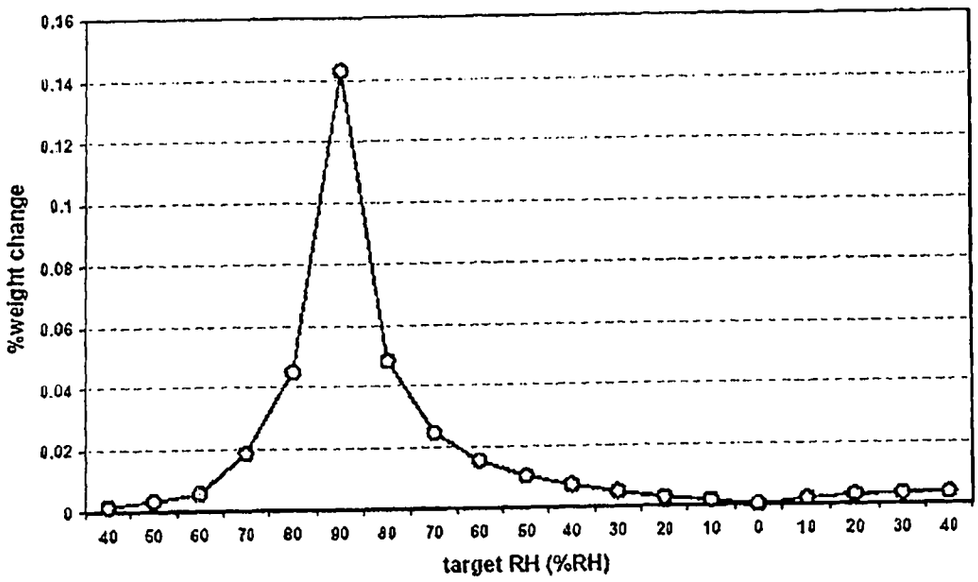

0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
%weight change
40 50 60 70 80 90 80 70 60 50 40 30 20 10 0 10 20 30 40
target RH (%RH)

Figure 3

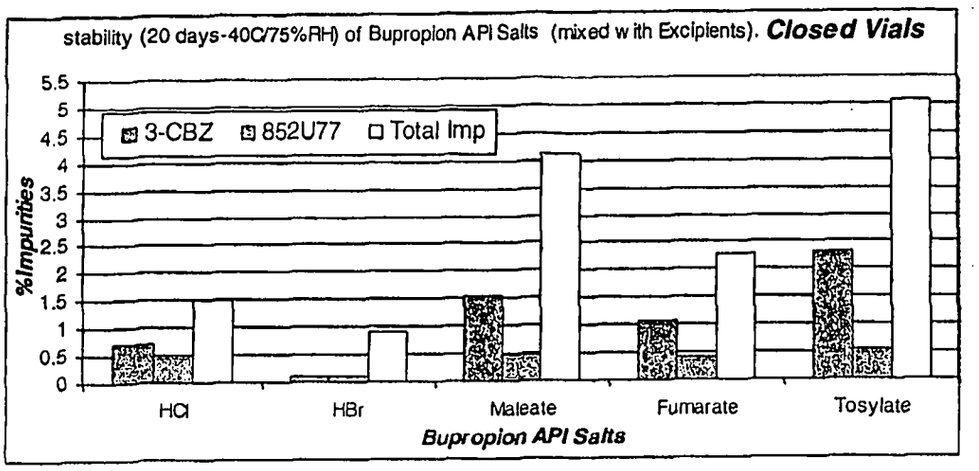

stability (20 days-40C/75%RH) of Bupropion API Salts (mixed with Excipients). Closed Vials
3-CBZ
852U77
Total Imp
%Impurities
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
HCl
HBr
Maleate
Fumarate
Tosylate
Bupropion API Salts

Figure 4

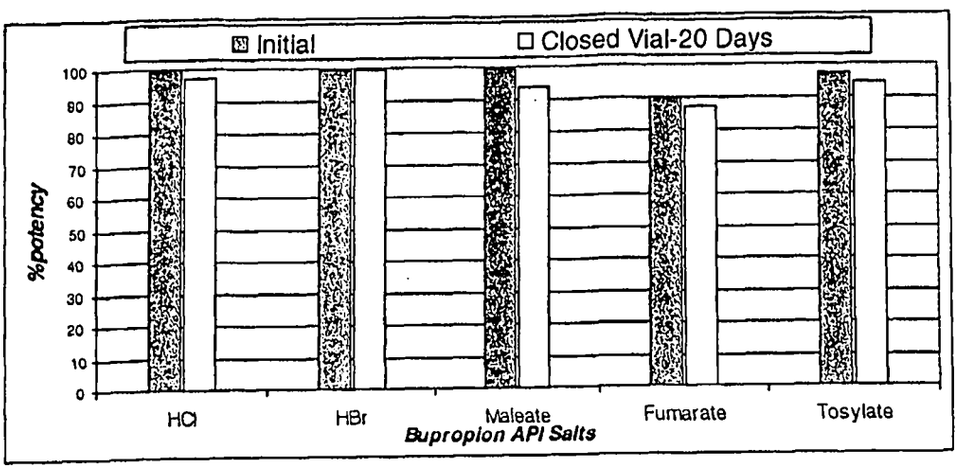

Initial
Closed Vial-20 Days
%potency
100
90
80
70
60
50
40
30
20
10
0
HCl
HBr
Maleate
Fumarate
Tosylate
Bupropion API Salts

Figure 5

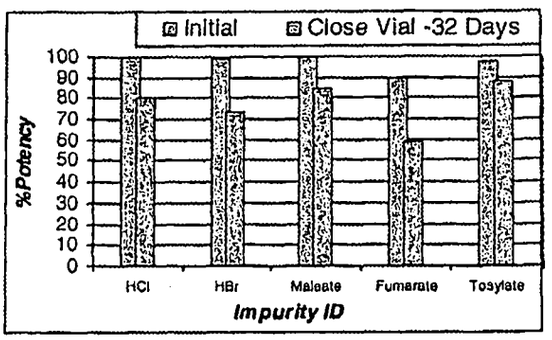

Initial
Close Vial -32 Days
100
90
80
70
60
50
40
30
20
10
0
%Potency
HCl
HBr
Maleate
Fumarate
Tosylate
Impurity ID

Figure 6

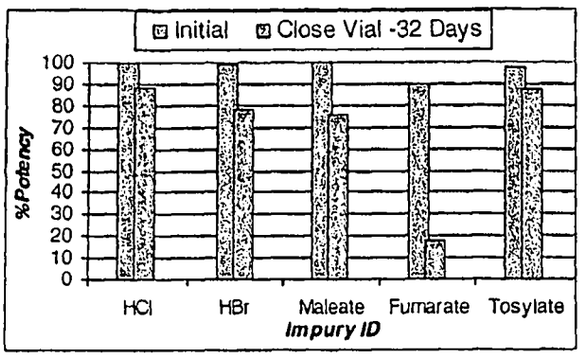

Initial
Close Vial -32 Days
100
90
80
70
60
50
40
30
20
10
0
%Potency
HCl
HBr
Maleate
Fumarate
Tosylate
Impury ID

Figure 7

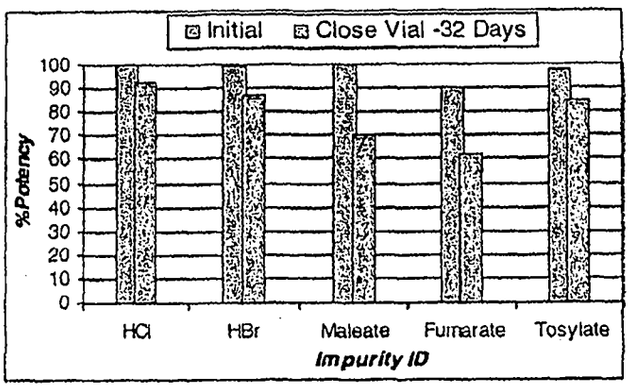
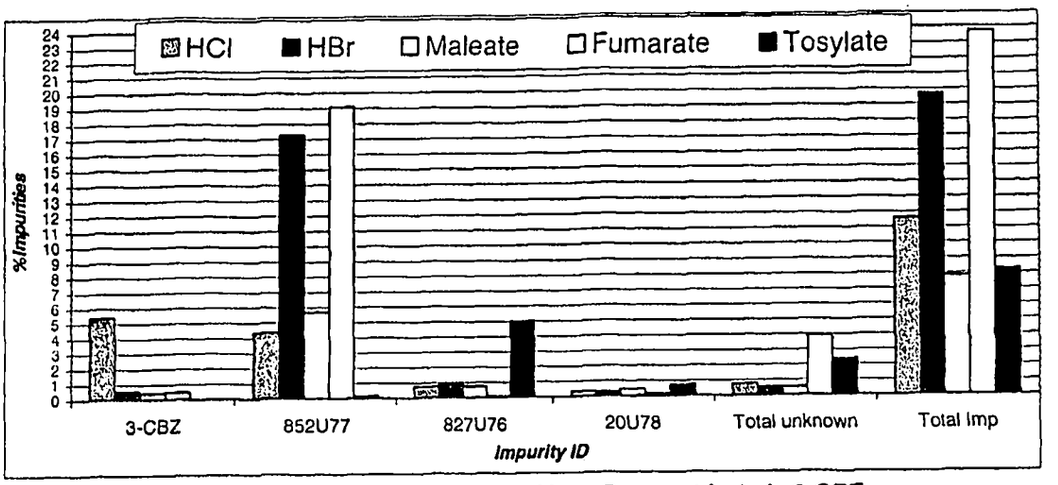
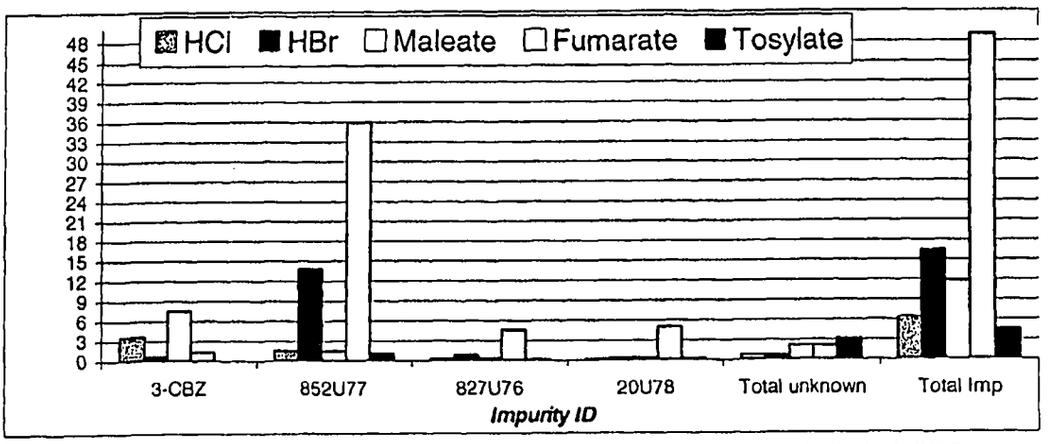

Initial
Close Vial -32 Days
100
90
80
70
60
50
40
30
20
10
0
% Potency
HCl
HBr
Maleate
Fumarate
Tosylate
Impurity ID

Figure 8



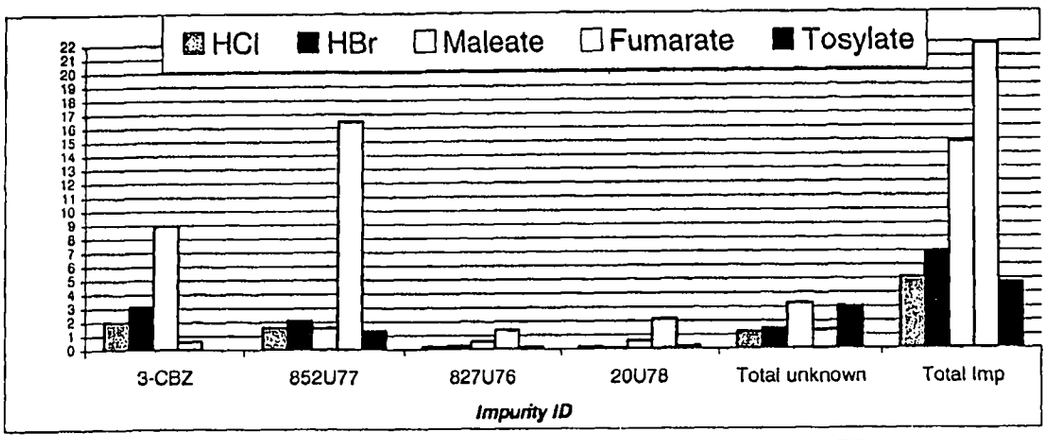
3-CBZ in Tosylate co elutes with p-Tsa peak. Toal Imp. Does not include 3-CBZ

Figure 9



3-CBZ in Tosylate co elutes with p-Tsa peak. Toal Imp. Does not include 3-CBZ

Figure 10



3-CBZ in Tosylate co elutes with p-Tsa peak. Toal Imp. Does not include 3-CBZ

Figure 11

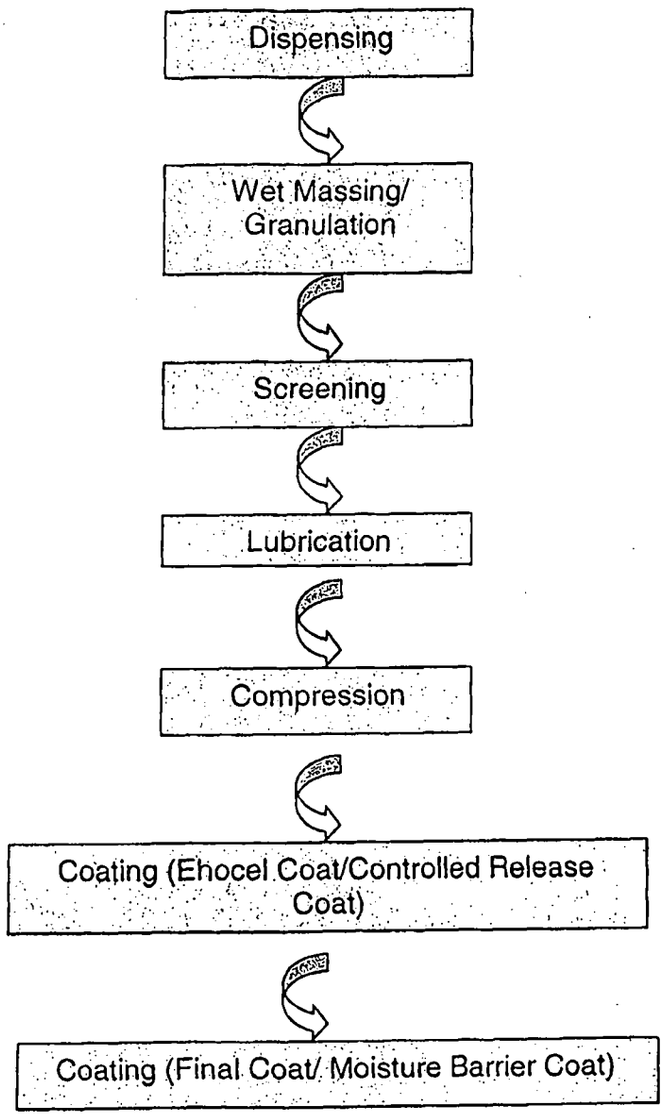

Dispensing
Wet Massing/ Granulation
Screening
Lubrication
Compression
Coating (Ehocel Coat/Controlled Release Coat)
Coating (Final Coat/ Moisture Barrier Coat)

Figure 12

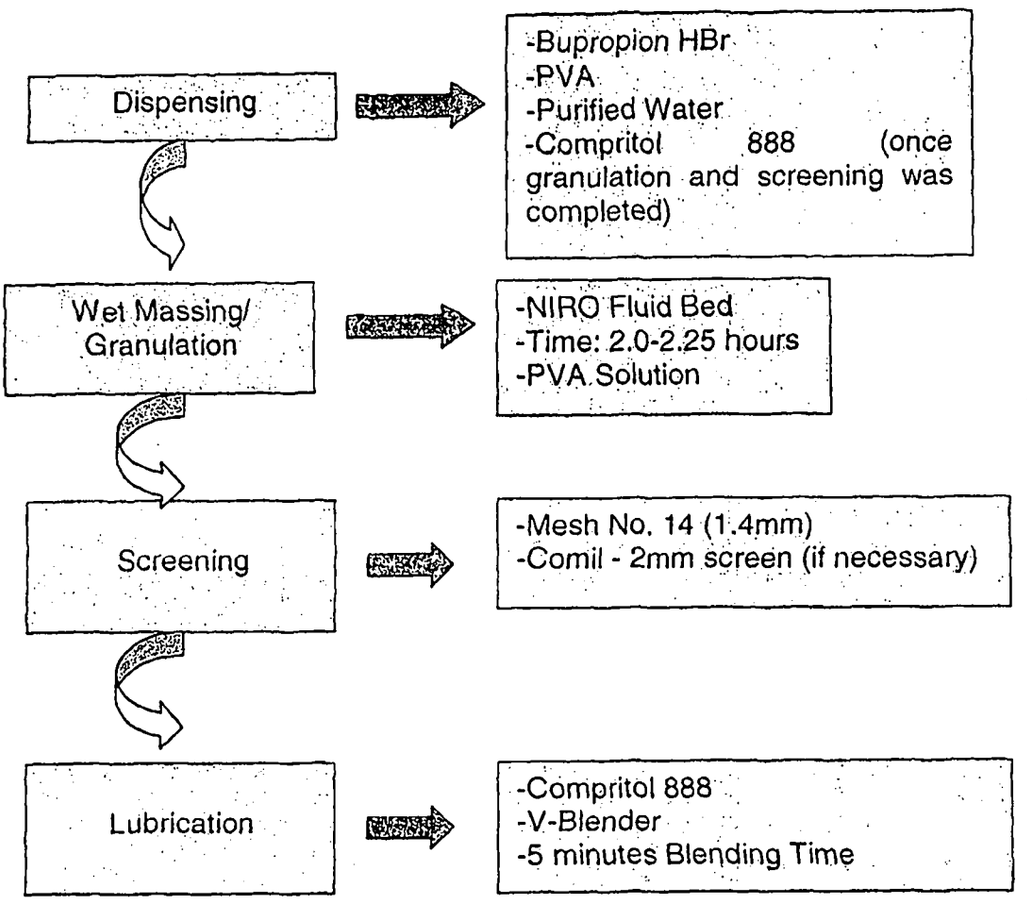

Dispensing
-Bupropion HBr
-PVA
-Purified Water
-Compritol 888 (once granulation and screening was completed)
Wet Massing/ Granulation
-NIRO Fluid Bed
-Time: 2.0-2.25 hours
-PVA Solution
Screening
-Mesh No. 14 (1.4mm)
-Comil - 2mm screen (if necessary)
Lubrication
-Compritol 888
-V-Blender
-5 minutes Blending Time

Figure 13

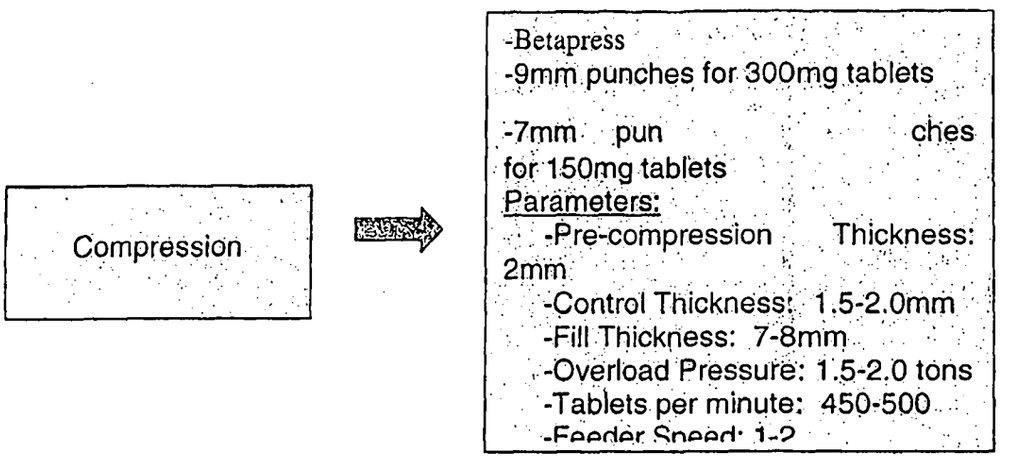

Compression
-Betapress
-9mm punches for 300mg tablets
-7mm pun ches for 150mg tablets
Parameters:
-Pre-compression Thickness: 2mm
-Control Thickness: 1.5-2.0mm
-Fill Thickness: 7-8mm
-Overload Pressure: 1.5-2.0 tons
-Tablets per minute: 450-500
-Feeder Speed: 1-2

Figure 14

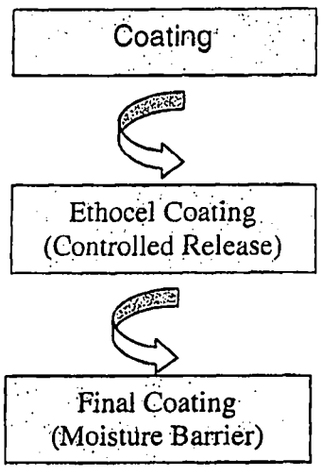

Coating
Ethocel Coating
(Controlled Release)
Final Coating
(Moisture Barrier)

Figure 15

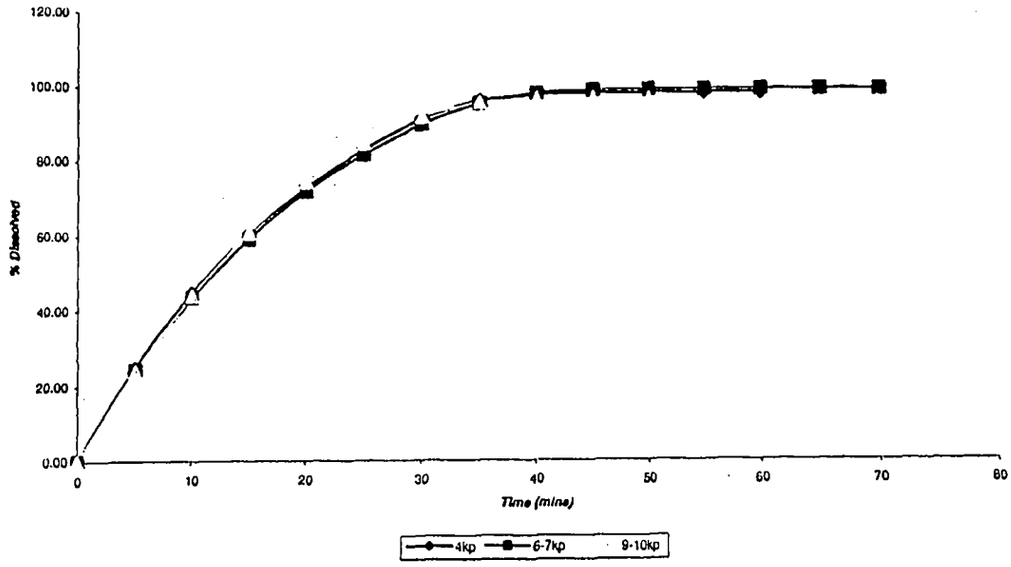

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
10
20
30
40
50
60
70
80
Time (mins)
4kp
6-7kp
9-10kp

Figure 16

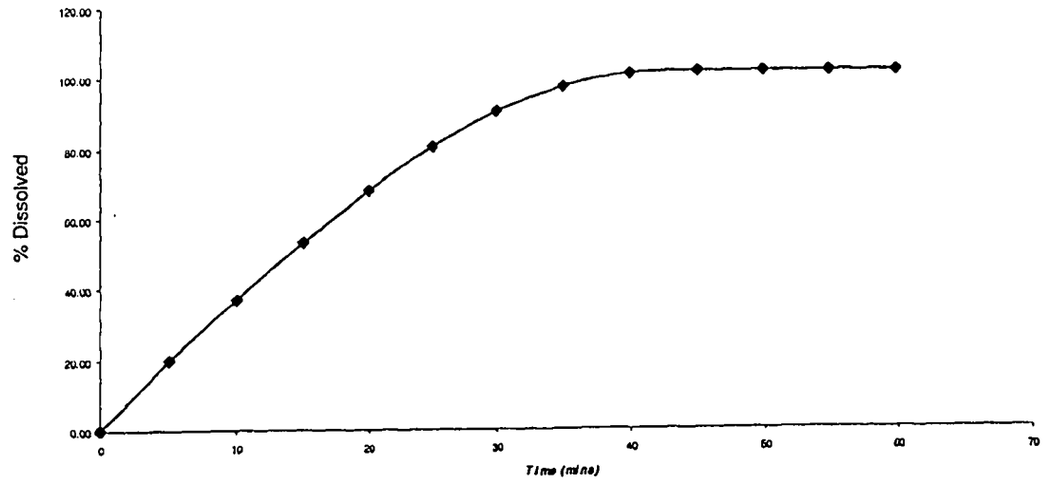

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
10
20
30
40
50
60
70
Time (mins)

Figure 17

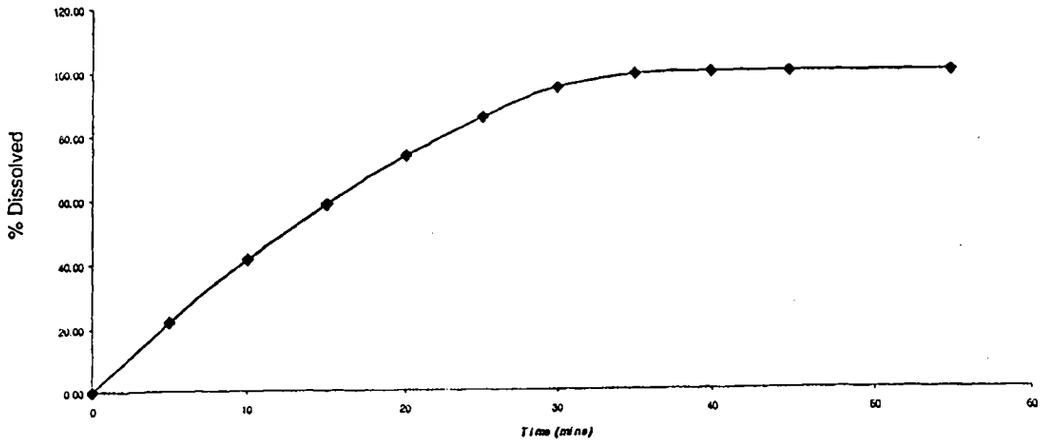

% Dissolved
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
10
20
30
40
50
60
Time (mins)

Figure 18

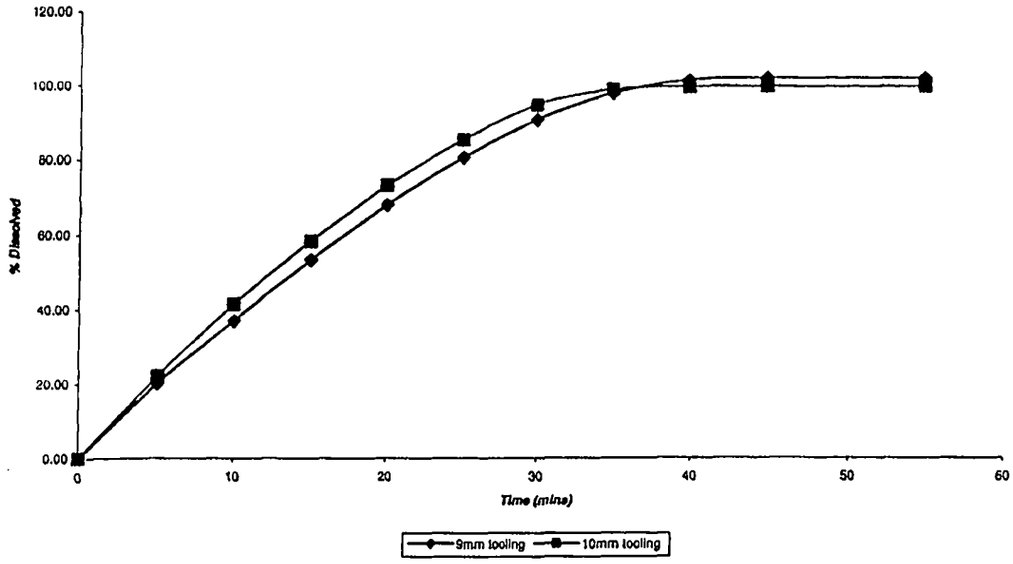

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
10
20
30
40
50
60
Time (mins)
9mm tooling
10mm tooling

Figure 19

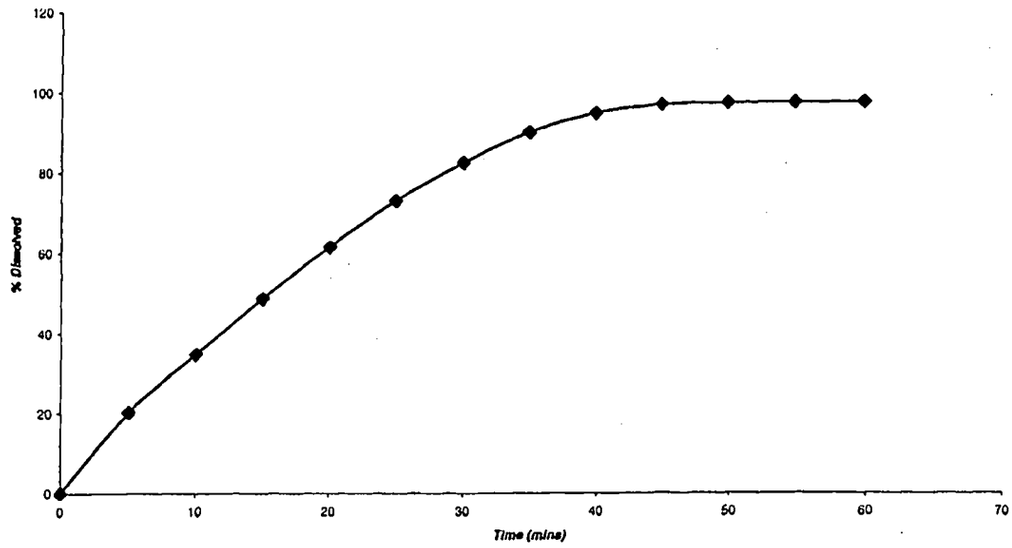


Figure 20

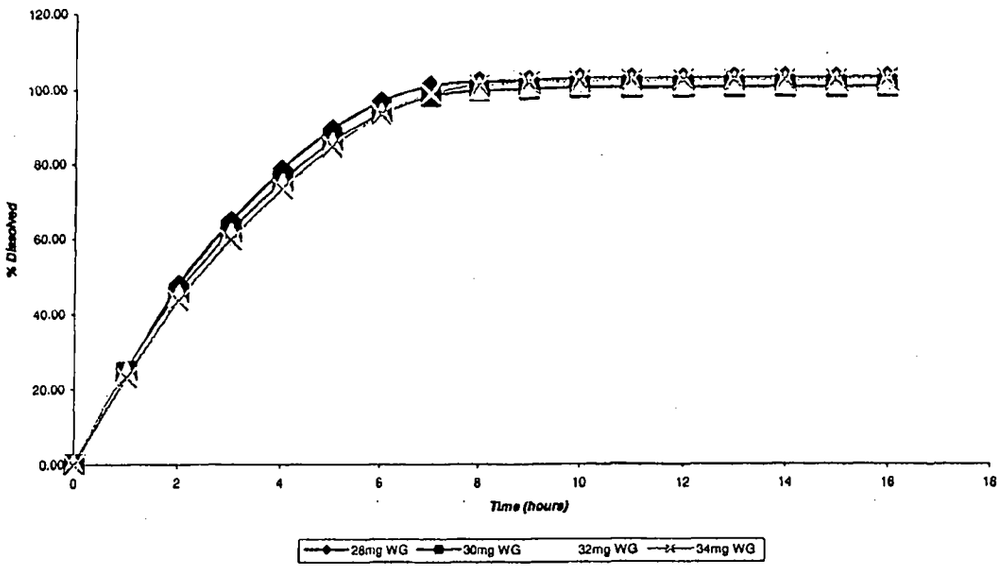

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
28mg WG
30mg WG
32mg WG
34mg WG

Figure 21

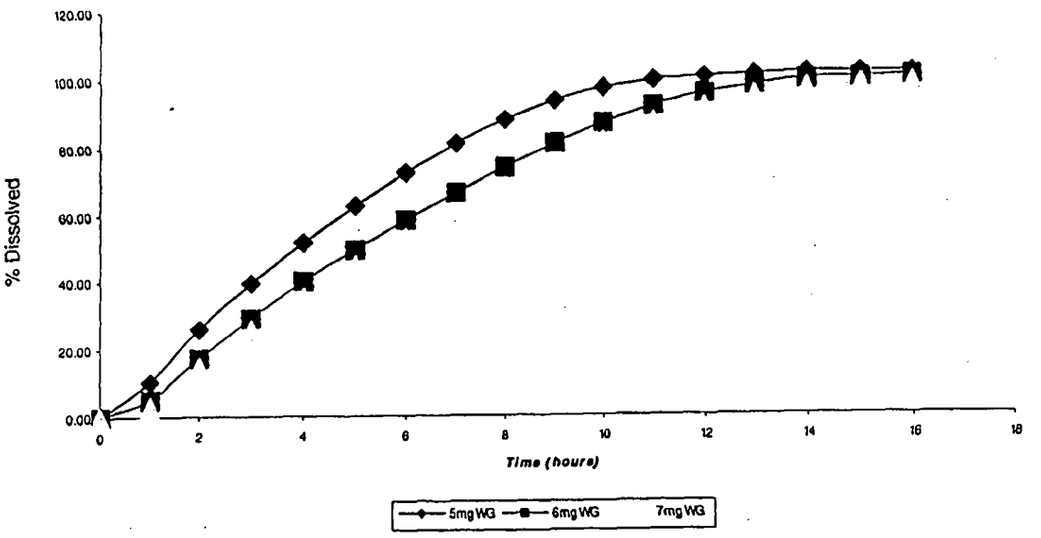

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (houre)
5mg WG
6mg WG
7mg WG

Figure 22

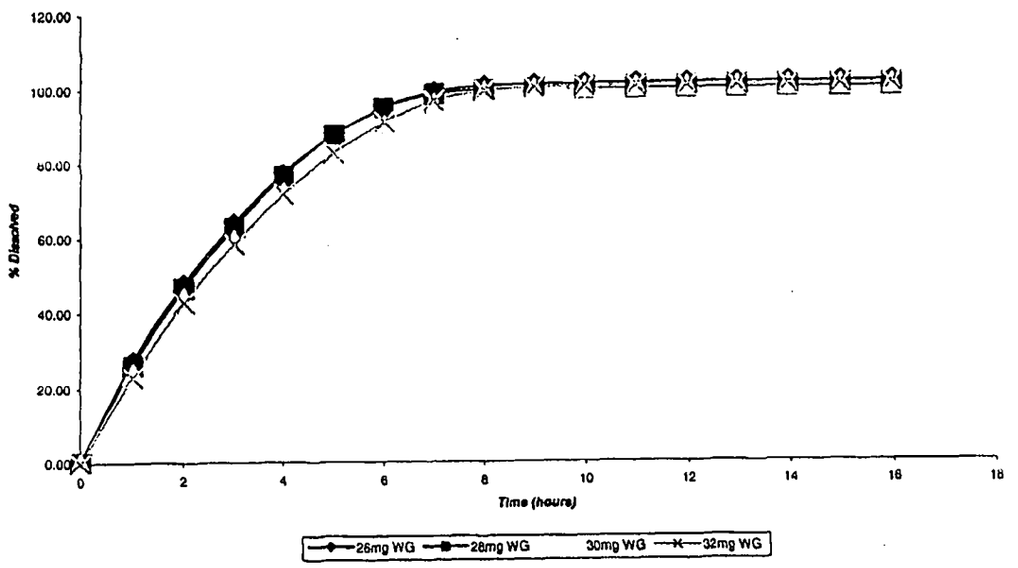

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
26mg WG
28mg WG
30mg WG
32mg WG

Figure 23

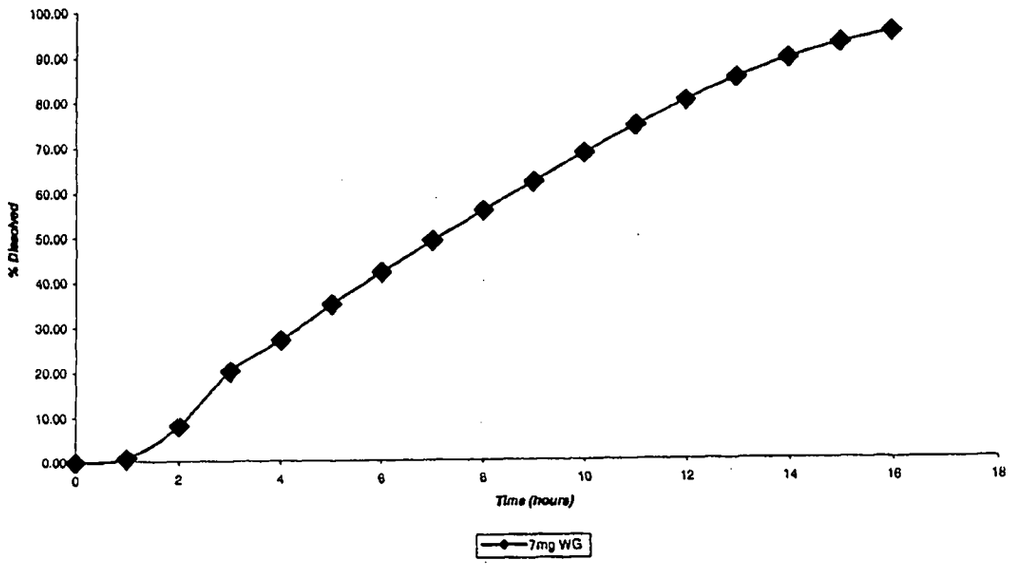

100.00
90.00
80.00
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
7mg WG

Figure 24

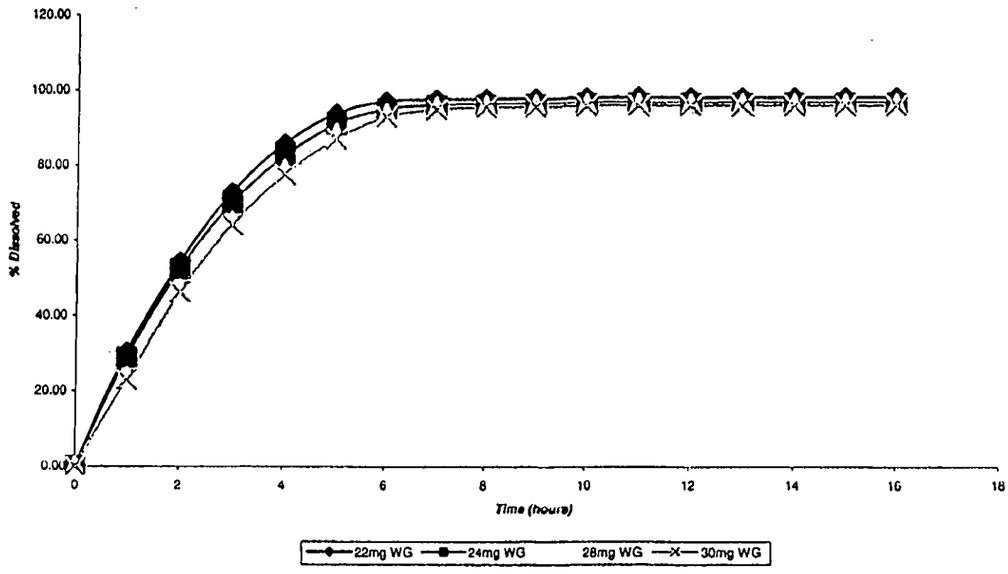

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
22mg WG
24mg WG
28mg WG
30mg WG

Figure 25

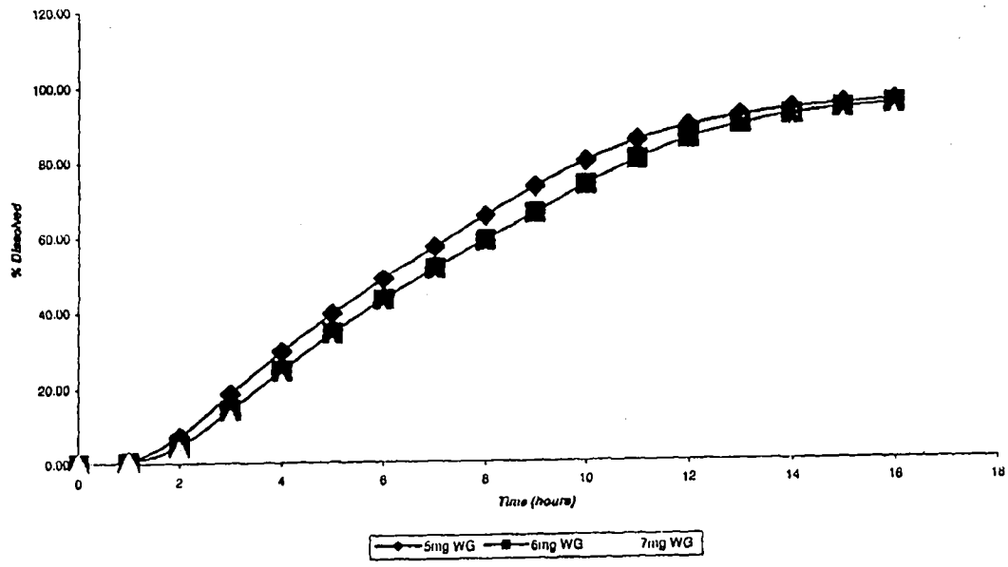

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
5mg WG
6mg WG
7mg WG

Figure 26

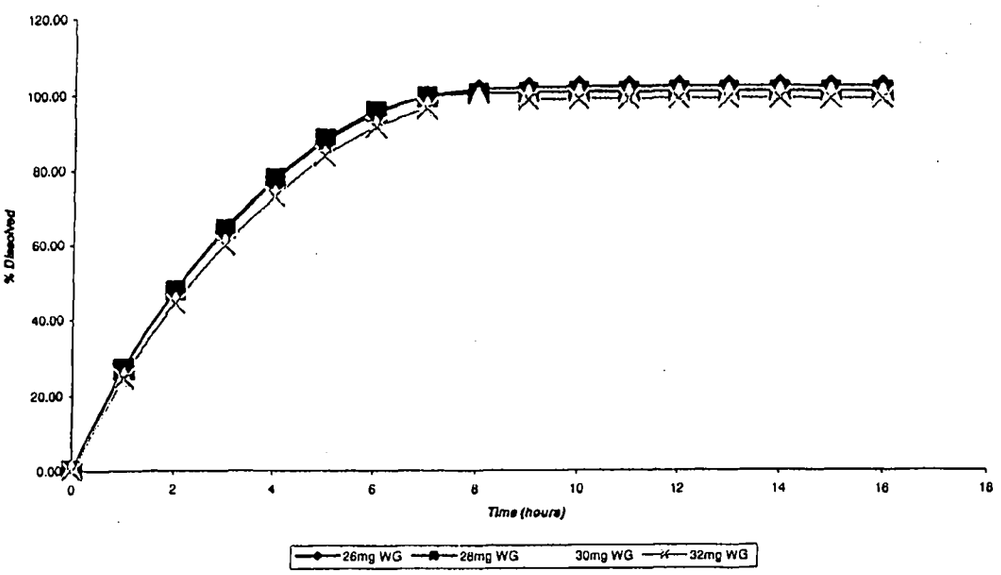

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
26mg WG
28mg WG
30mg WG
32mg WG

Figure 27

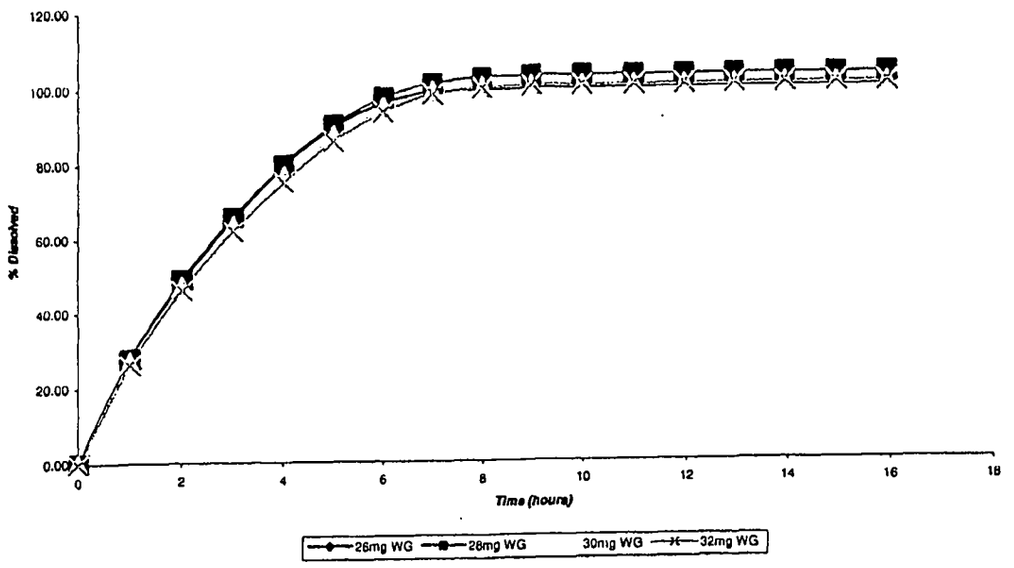

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
26mg WG
28mg WG
30mg WG
32mg WG

Figure 28

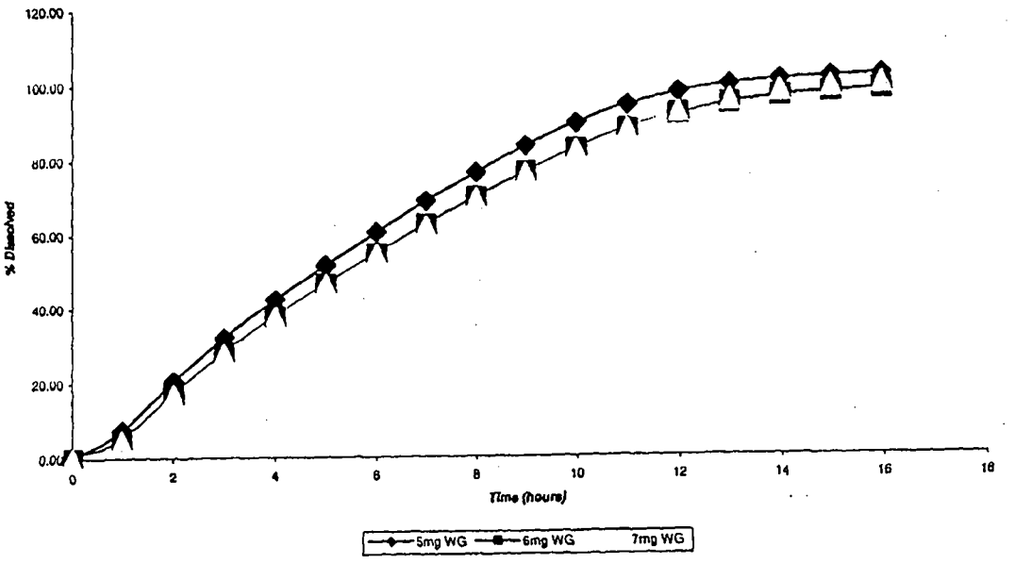

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
5mg WG
6mg WG
7mg WG

Figure 29

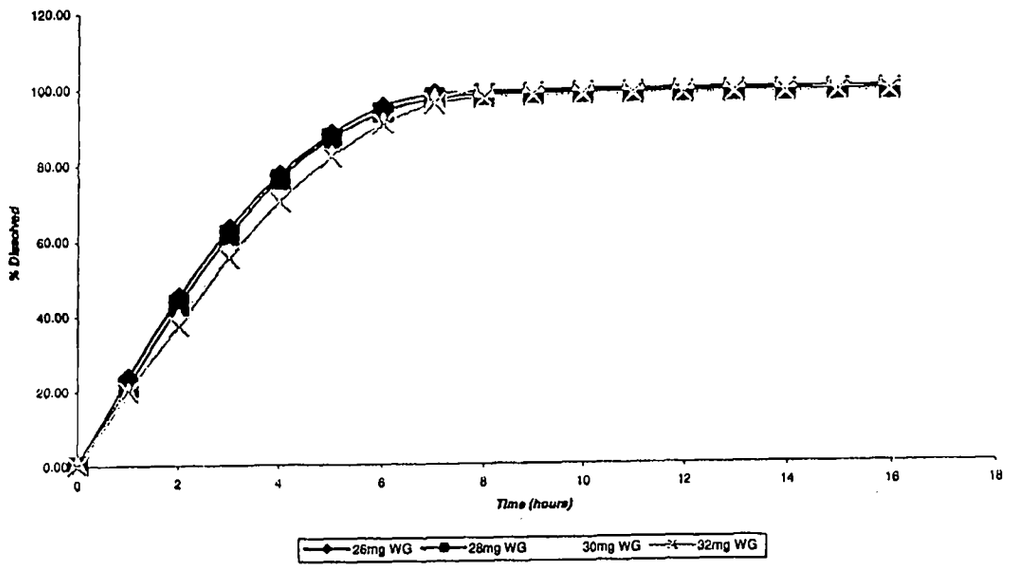

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
26mg WG
28mg WG
30mg WG
32mg WG

Figure 30

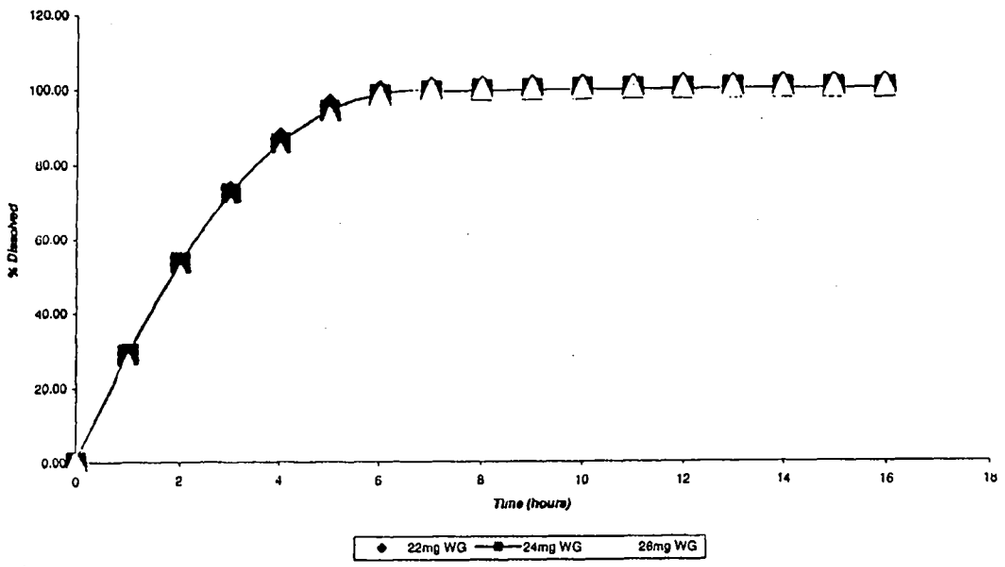

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
22mg WG
24mg WG
28mg WG

Figure 31

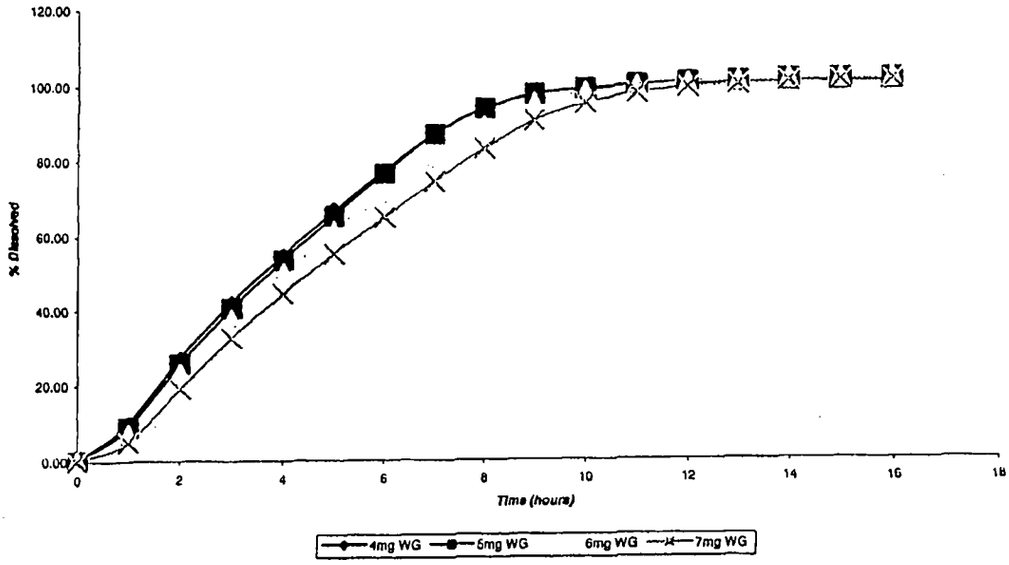

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
4mg WG
5mg WG
6mg WG
7mg WG

Figure 32

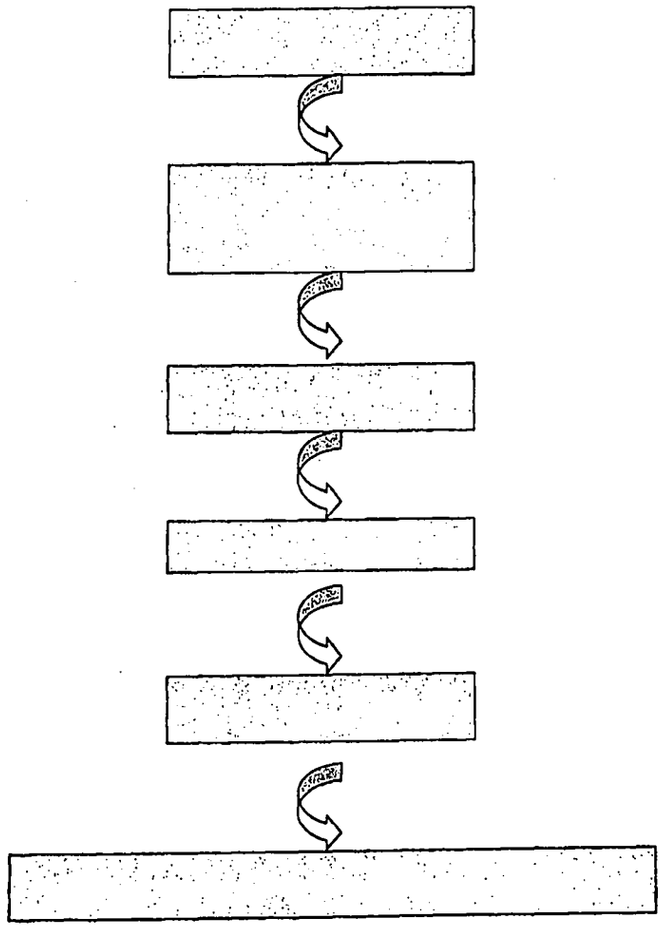


Figure 33

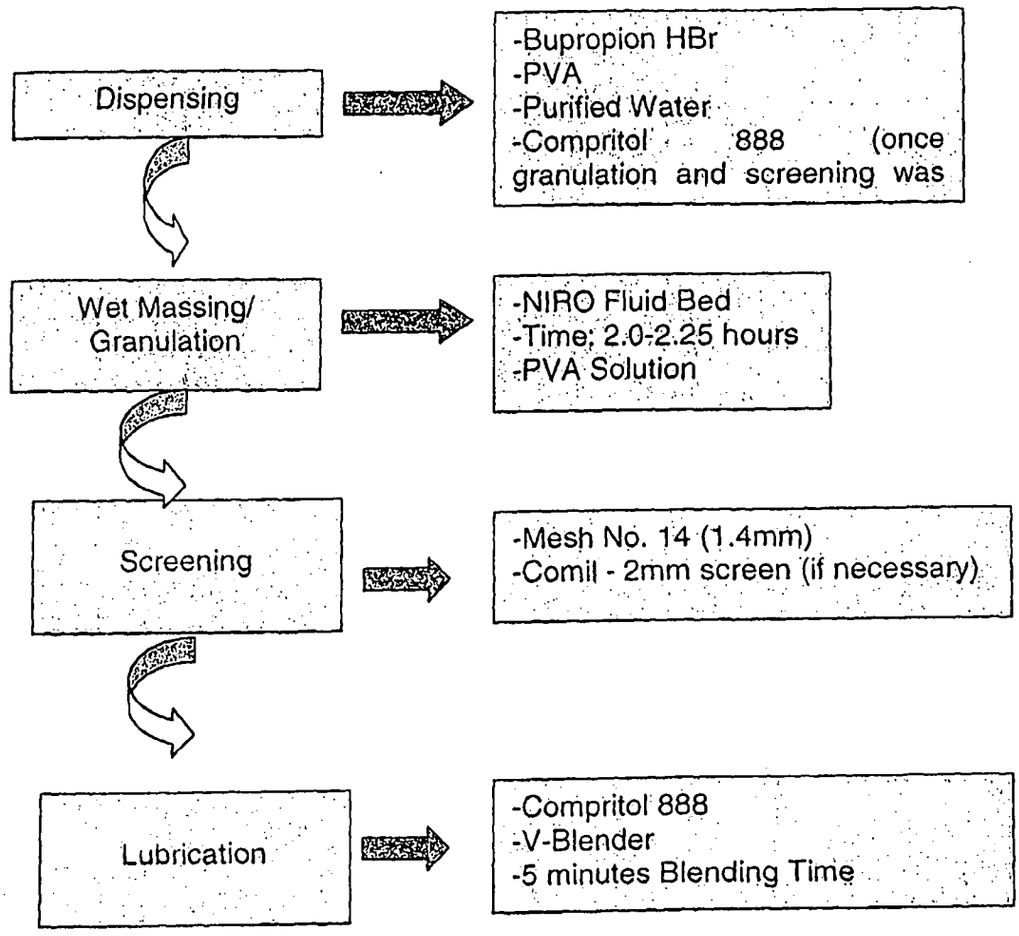

Dispensing
-Bupropion HBr
-PVA
-Purified Water
-Compritol 888 (once
granulation and screening was
Wet Massing/
Granulation
-NIRO Fluid Bed
-Time; 2.0-2.25 hours
-PVA Solution
Screening
-Mesh No. 14 (1.4mm)
-Comil - 2mm screen (if necessary)
Lubrication
-Compritol 888
-V-Blender
-5 minutes Blending Time

Figure 34

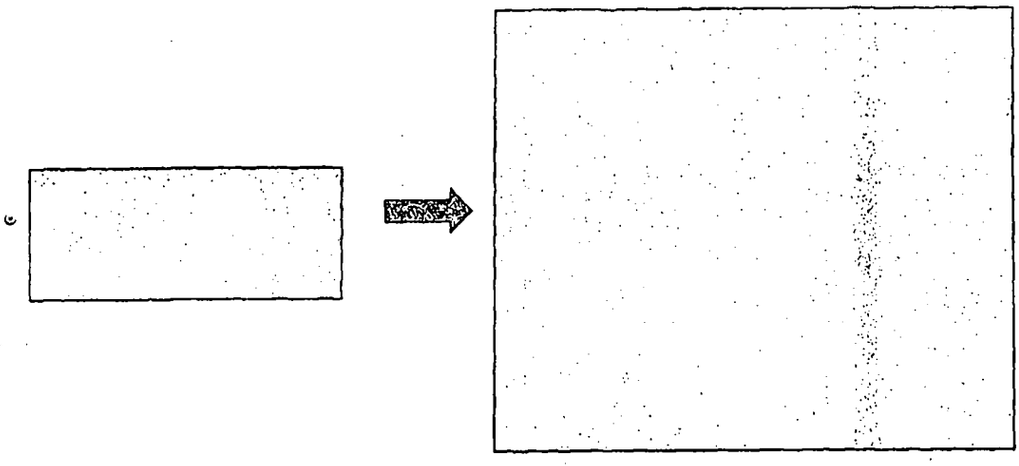


Figure 35

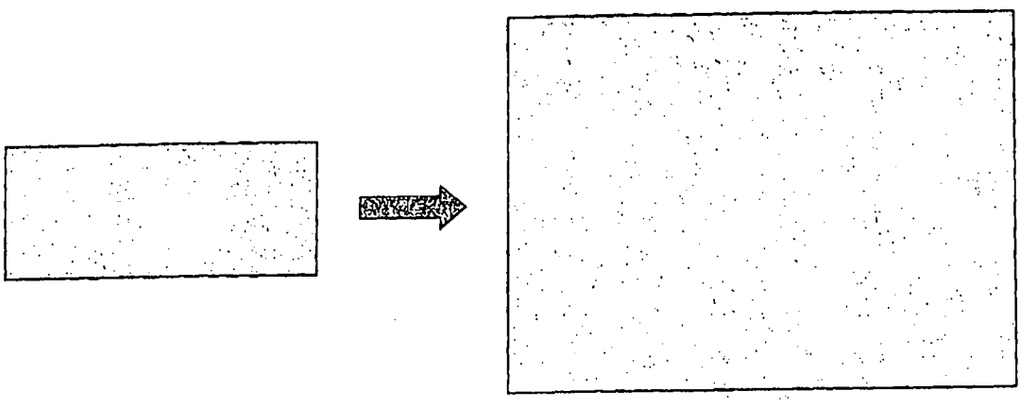


Figure 36

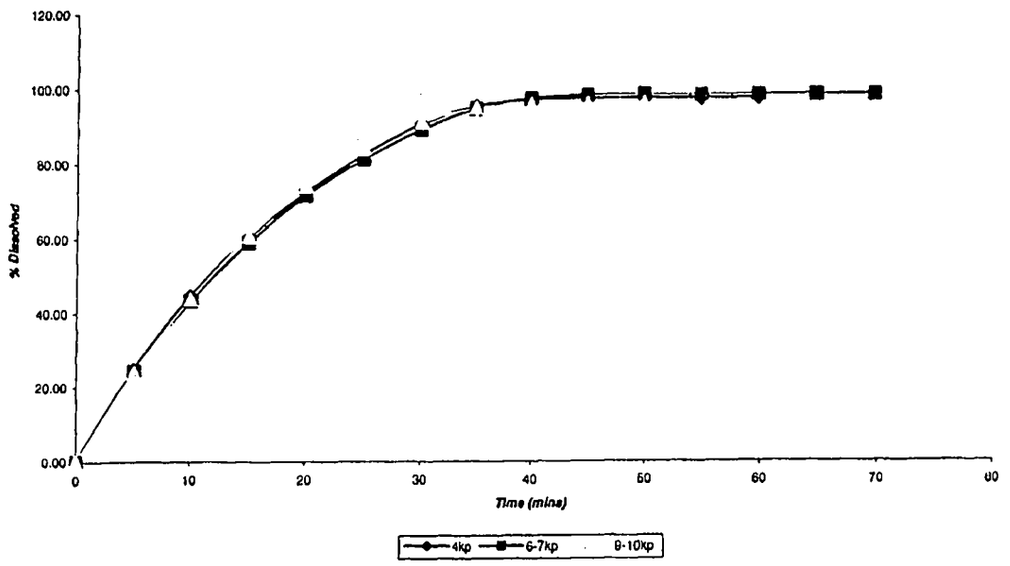

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
10
20
30
40
50
60
70
80
Time (mins)
4kp
6-7kp
8-10kp

Figure 37

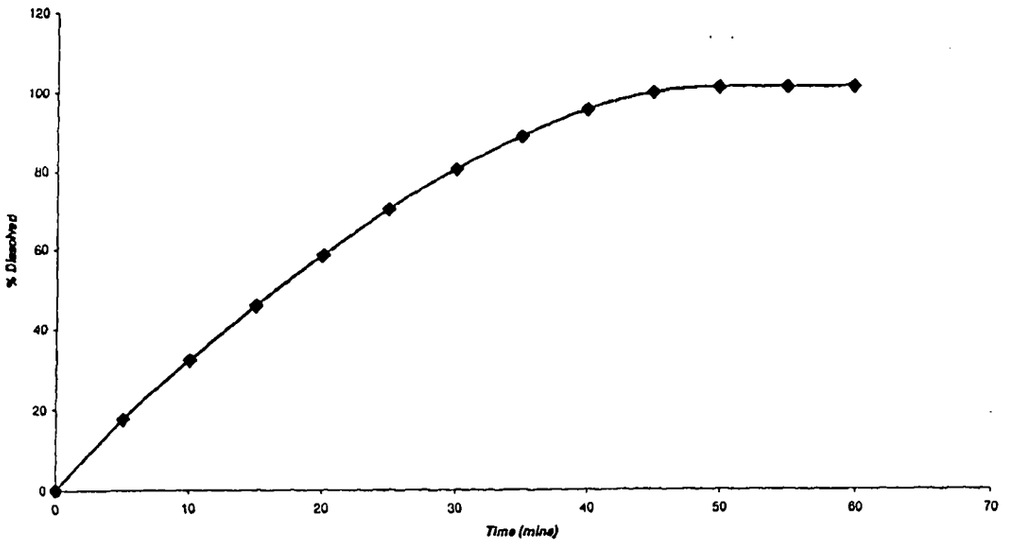


Figure 38

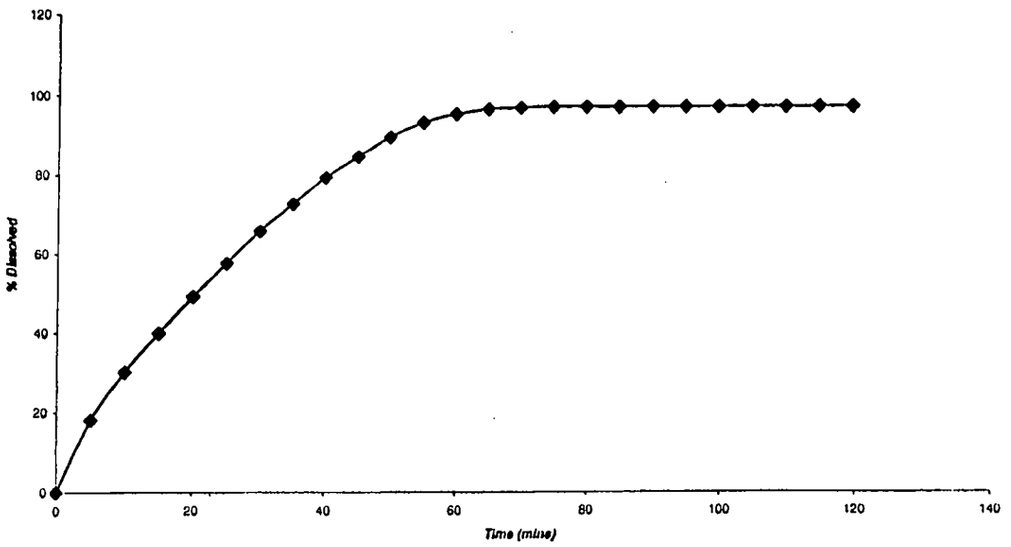

120
100
80
60
40
20
0
% Dissolved
0
20
40
60
80
100
120
140
Time (mins)

Figure 39

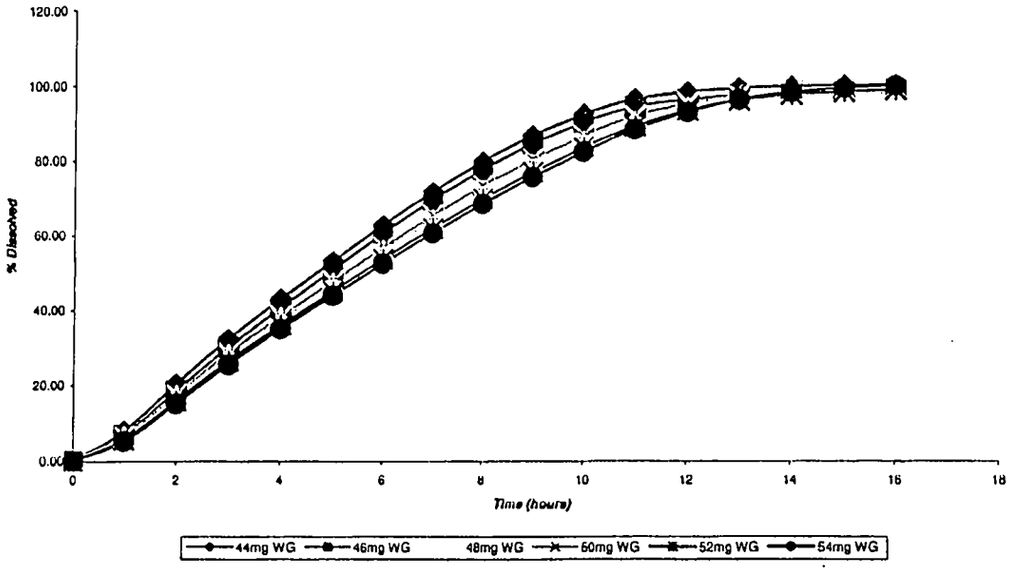

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
44mg WG
46mg WG
48mg WG
50mg WG
52mg WG
54mg WG

Figure 40

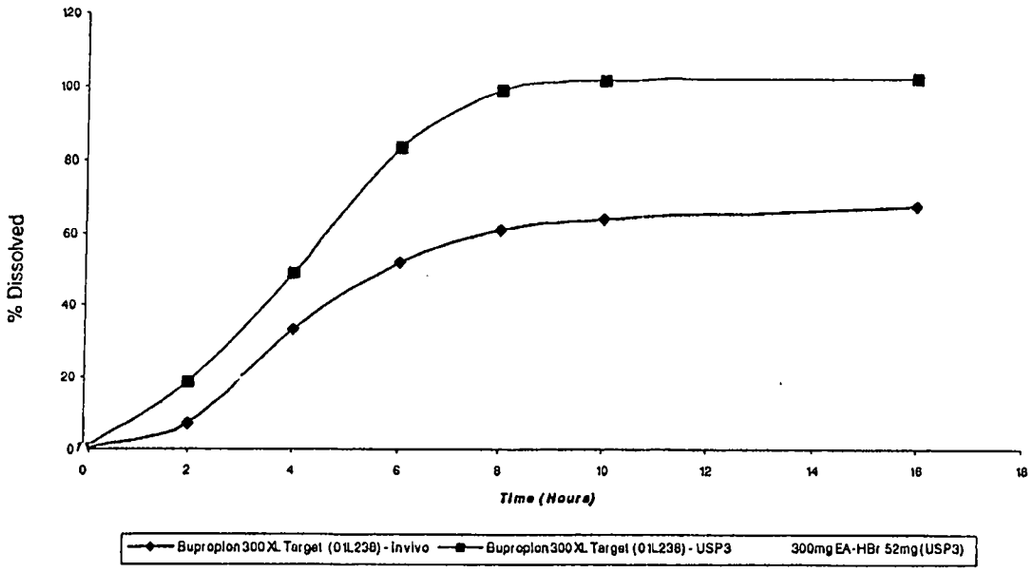

120
100
80
60
40
20
0
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (Hours)
Bupropion 300 XL Target (01L236) - Invivo
Bupropion 300 XL Target (01L236) - USP3
300mg EA-HBr 52mg (USP3)

Figure 41

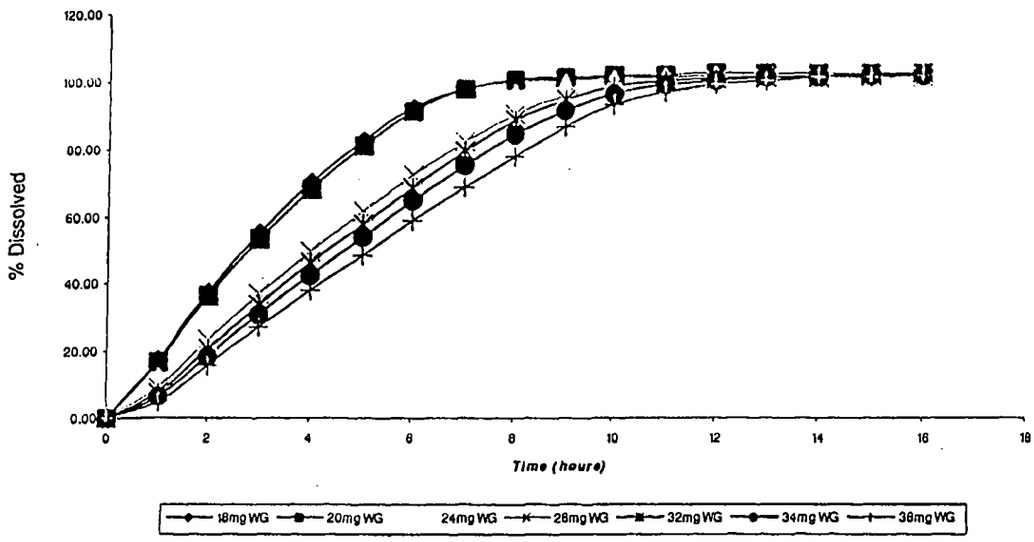

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
18mg WG
20mg WG
24mg WG
28mg WG
32mg WG
34mg WG
36mg WG

Figure 42

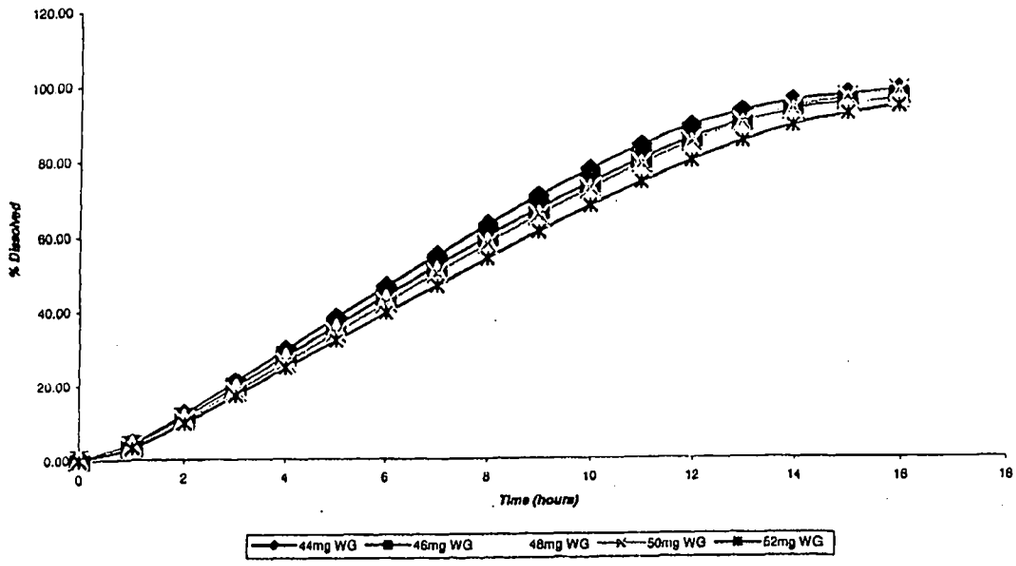

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
44mg WG
46mg WG
48mg WG
50mg WG
52mg WG

Figure 43

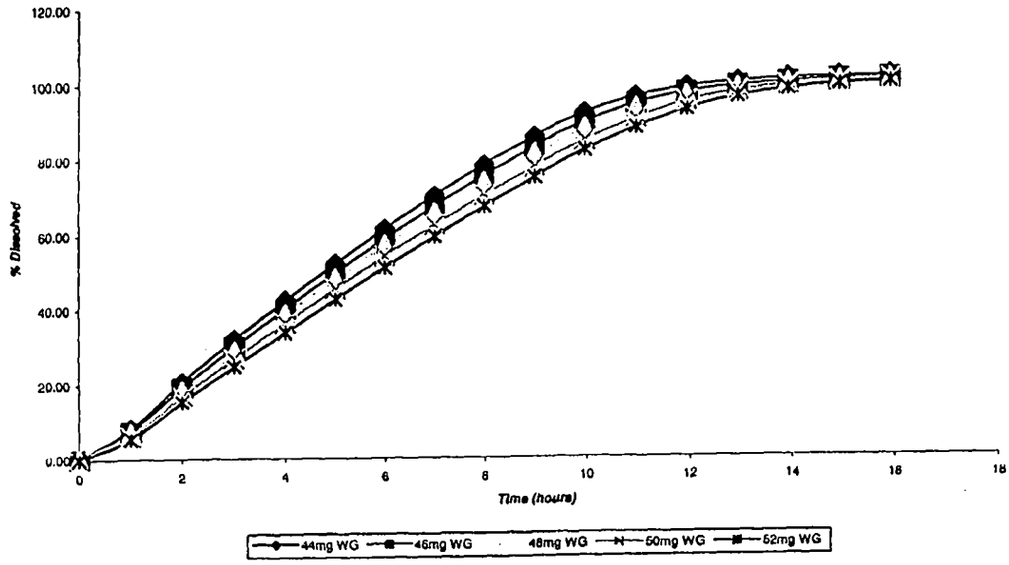

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
44mg WG
46mg WG
48mg WG
50mg WG
52mg WG

Figure 44

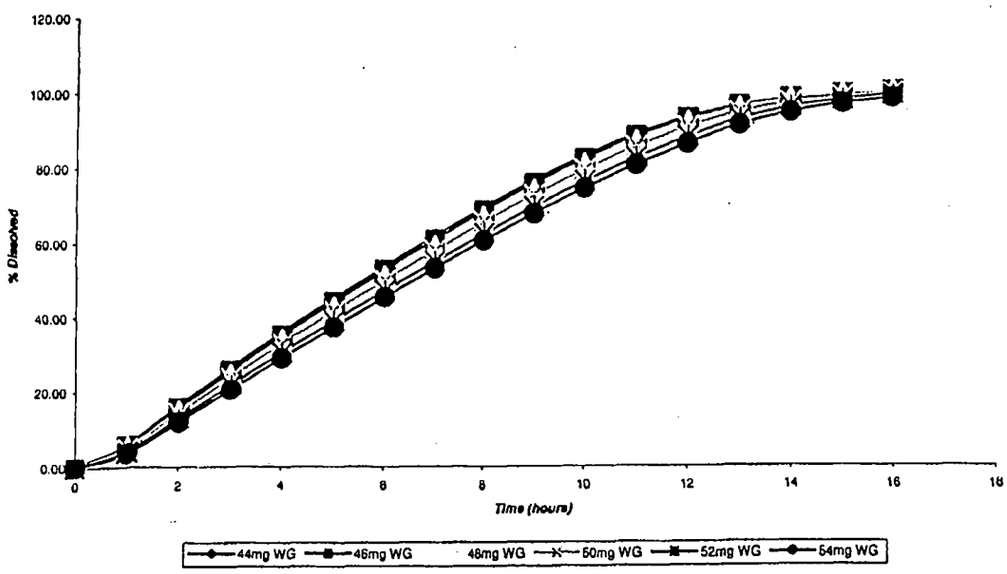

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
44mg WG
46mg WG
48mg WG
50mg WG
52mg WG
54mg WG

Figure 45

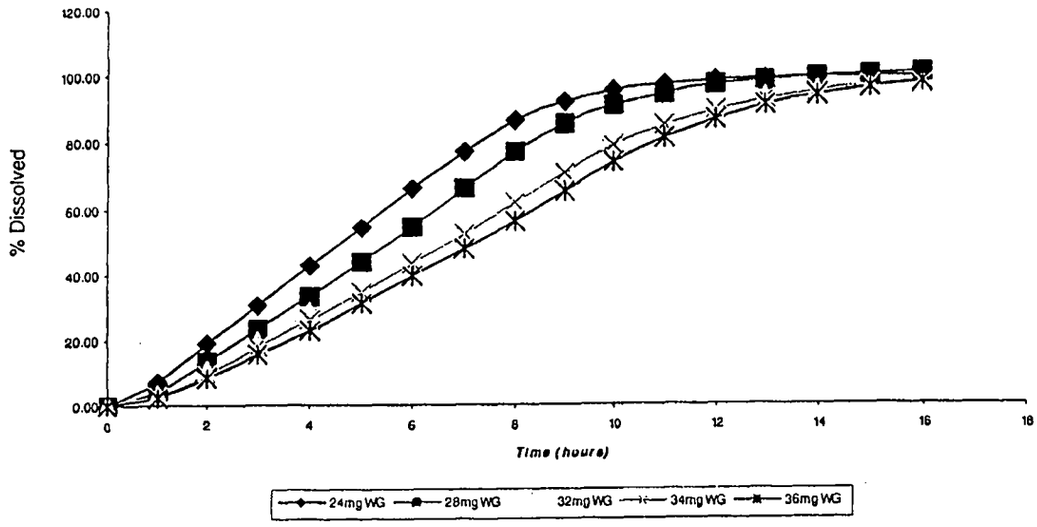

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (hours)
24mg WG
28mg WG
32mg WG
34mg WG
36mg WG

Figure 46

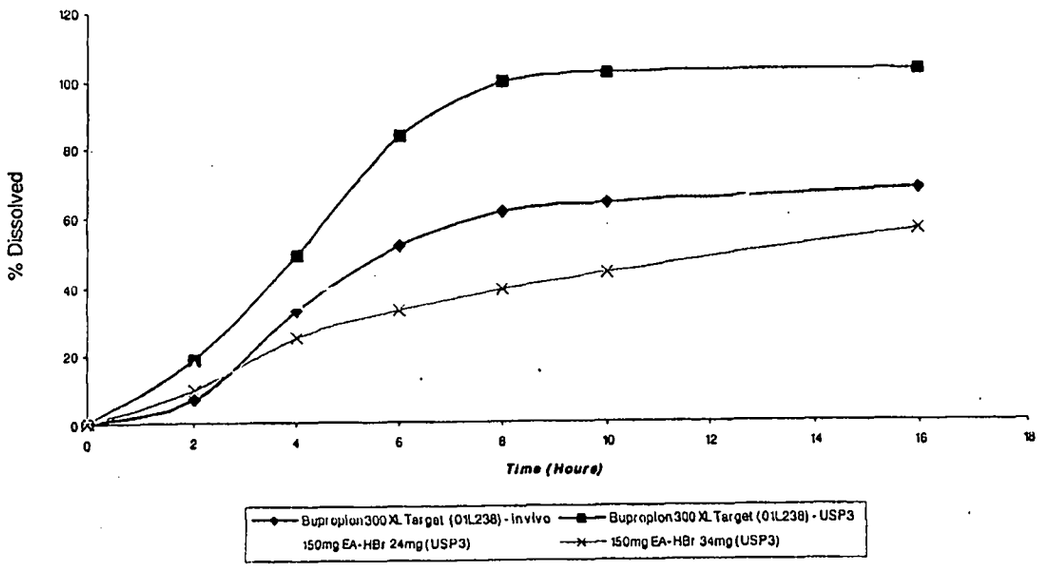

120
100
80
60
40
20
0
% Dissolved
0
2
4
6
8
10
12
14
16
18
Time (Hours)
Bupropion300 XL Target (01L238) - Invivo
Bupropion300 XL Target (01L238) - USP3
150mg EA-HBr 24mg (USP3)
150mg EA-HBr 34mg (USP3)

Figure 47

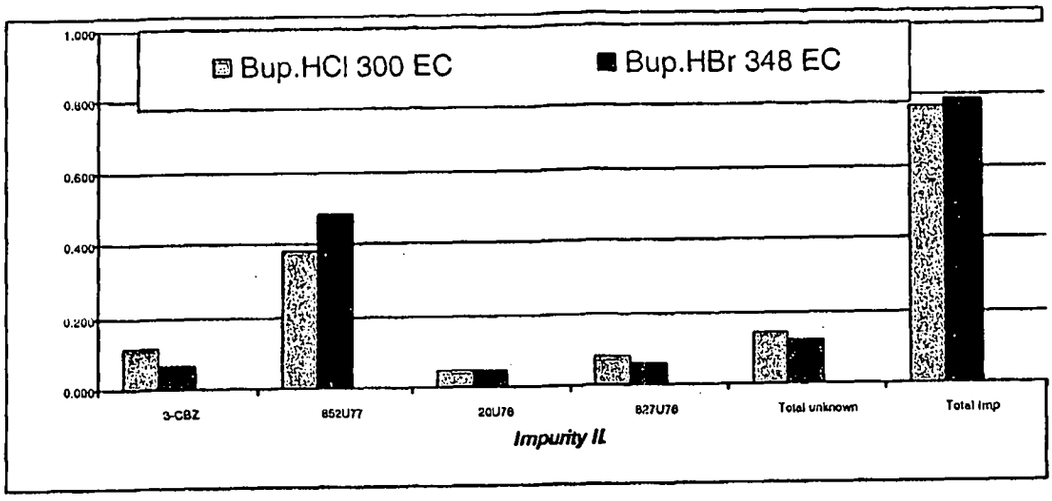

Bup.HCl 300 EC
Bup.HBr 348 EC
1.000
0.800
0.600
0.400
0.200
0.000
3-CBZ
852U77
20U78
827U78
Total unknown
Total Imp
Impurity IL

Figure 48

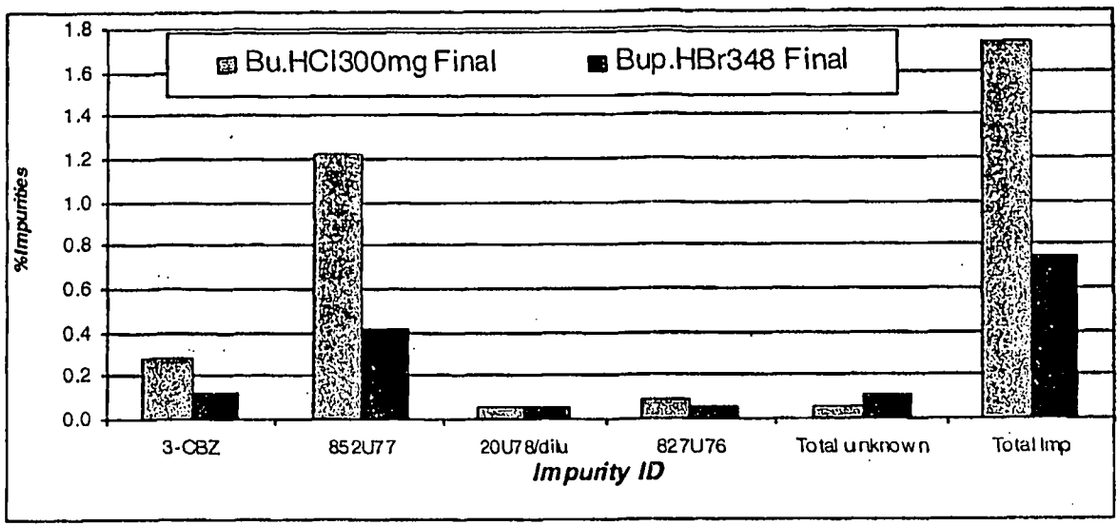
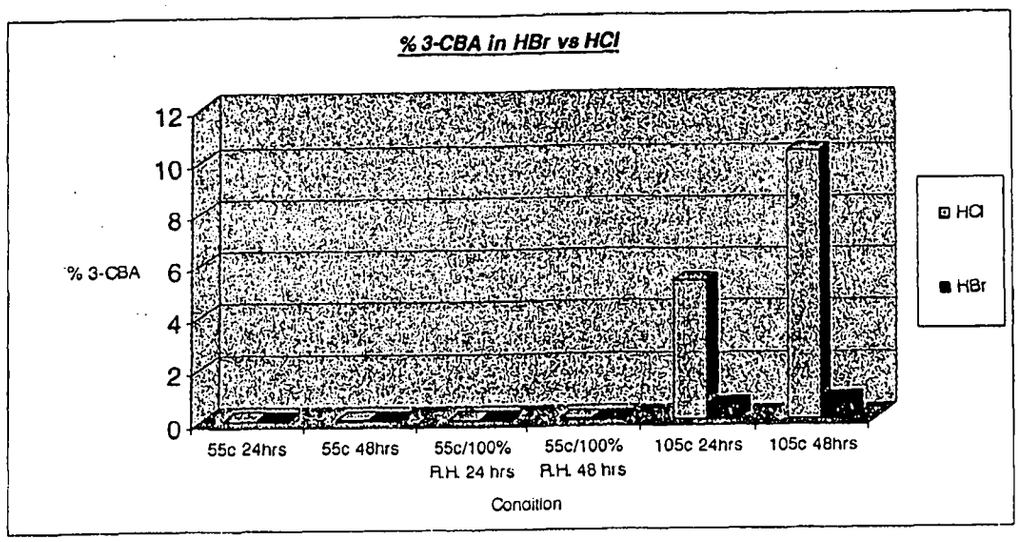

Bu.HCl300mg Final
Bup.HBr348 Final
%Impurities
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
3-CBZ
852U77
20U78/dilu
827U76
Total unknown
Total Imp
Impurity ID

Figure 49


% 3-CBA in HBr vs HCl
12
10
8
6
4
2
0
% 3-CBA
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
105c 24hrs
105c 48hrs
Condition
HCl
HBr

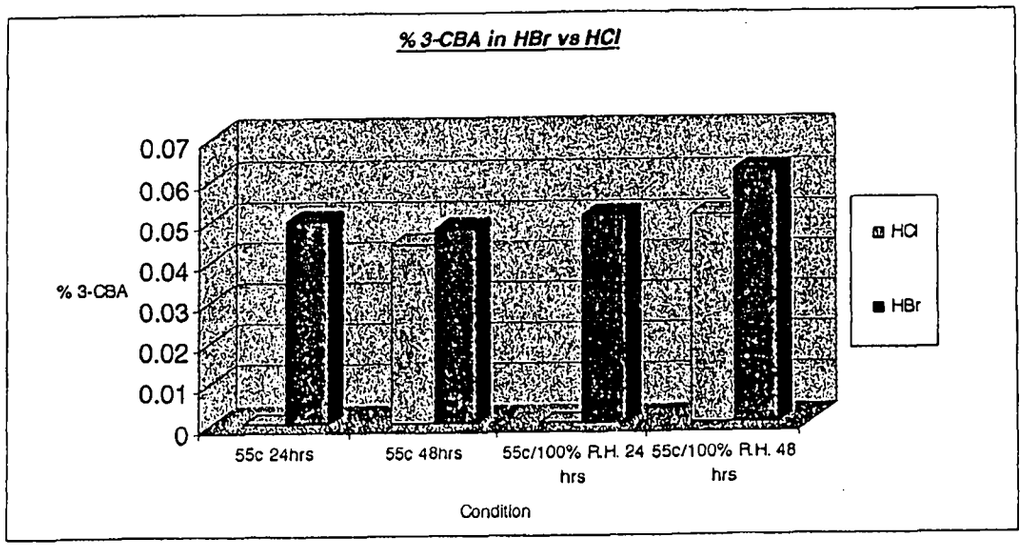
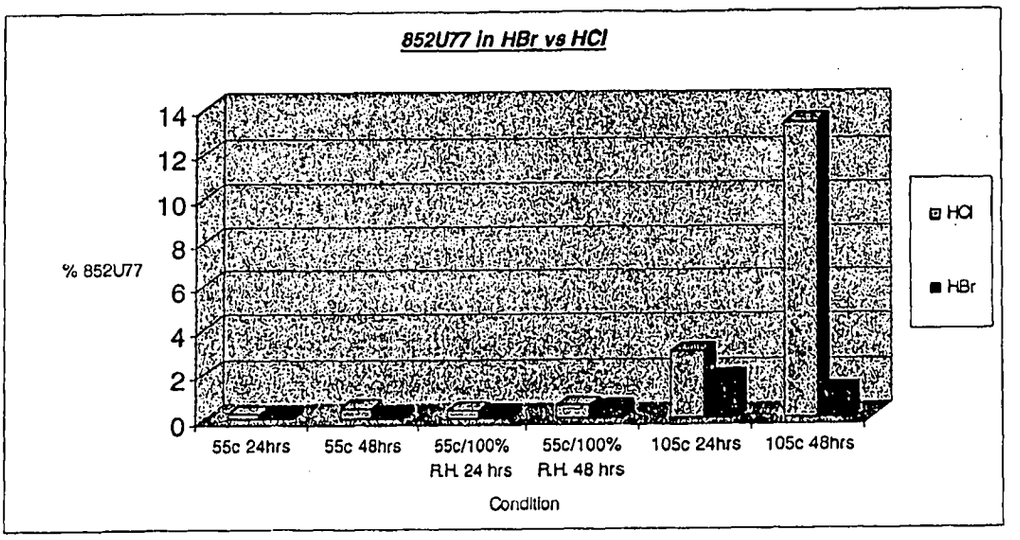

% 3-CBA in HBr vs HCl
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
% 3-CBA
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
Condition
HCl
HBr

Figure 50


852U77 in HBr vs HCl
% 852U77
14
12
10
8
6
4
2
0
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
105c 24hrs
105c 48hrs
Condition
HCl
HBr

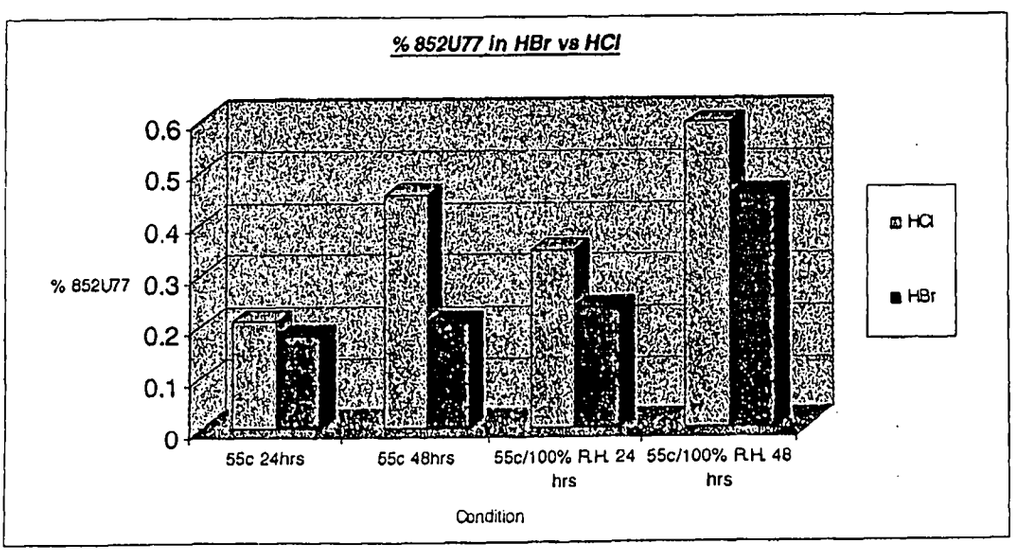
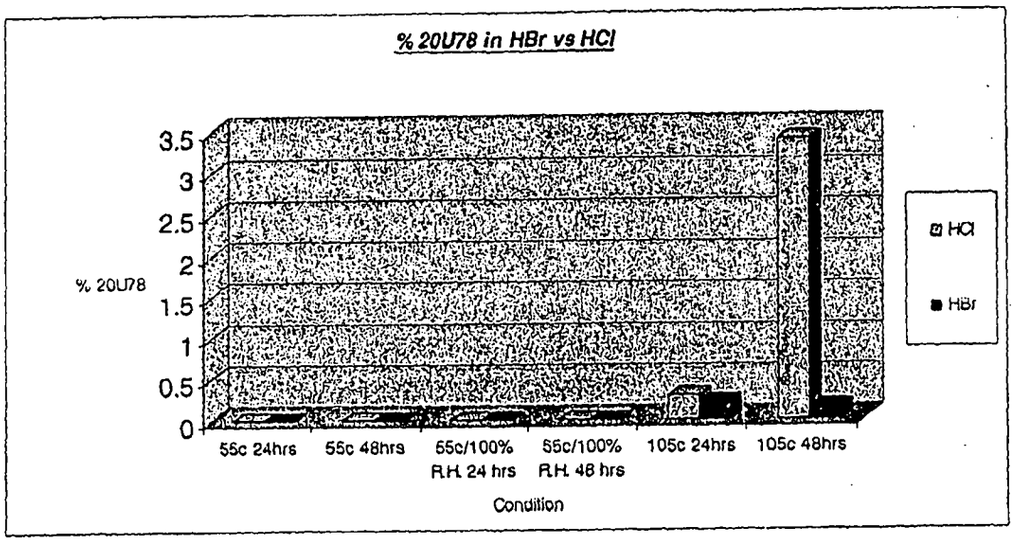

% 852U77 in HBr vs HCl
% 852U77
0.6
0.5
0.4
0.3
0.2
0.1
0
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
Condition
HCl
HBr

Figure 51


% 20U78 in HBr vs HCl
3.5
3
2.5
2
1.5
1
0.5
0
% 20U78
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
105c 24hrs
105c 48hrs
Condition
HCl
HBr

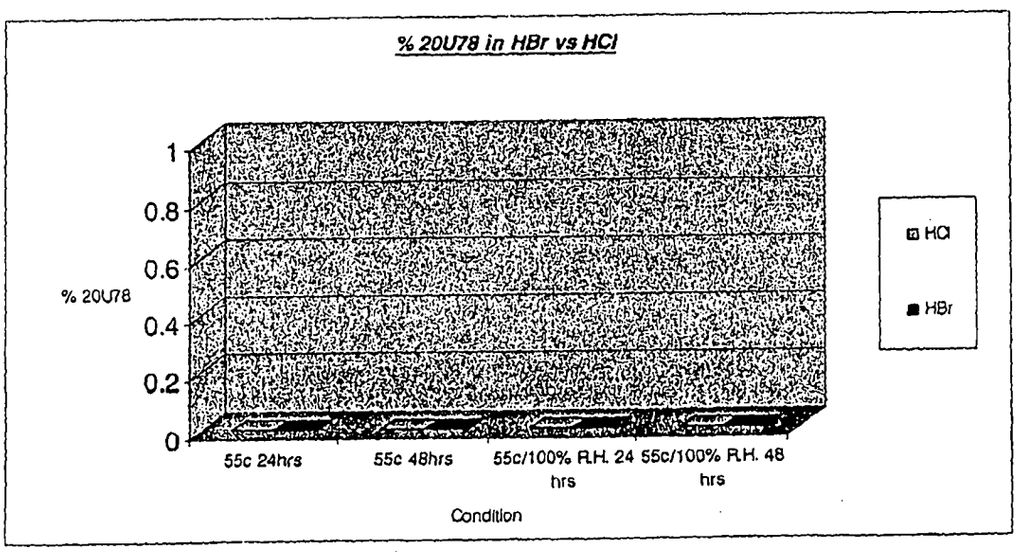
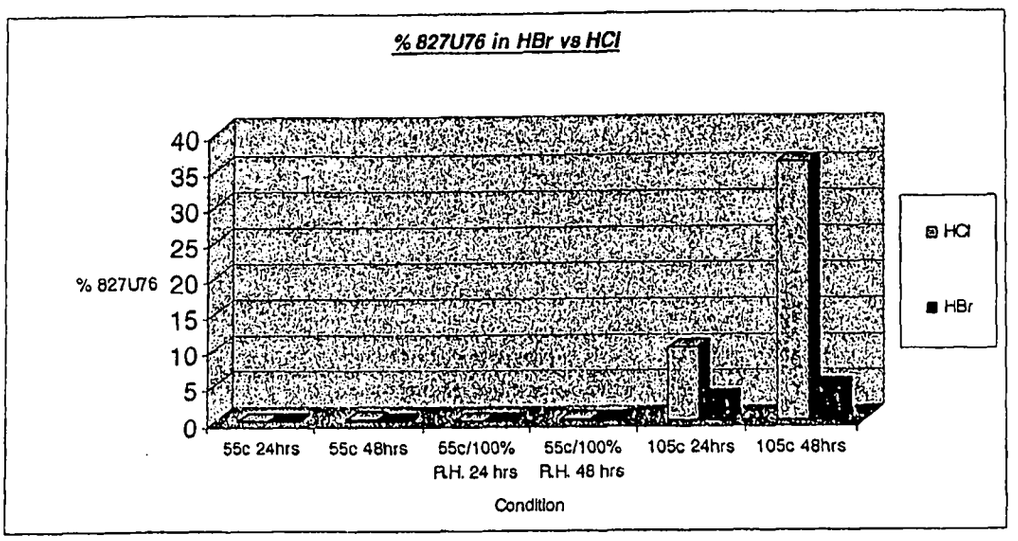

% 20U78 in HBr vs HCl
1
0.8
0.6
0.4
0.2
0
% 20U78
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
Condition
HCl
HBr

Figure 52


% 827U76 in HBr vs HCl
40
35
30
25
% 827U76 20
15
10
5
0
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
105c 24hrs
105c 48hrs
Condition
HCl
HBr

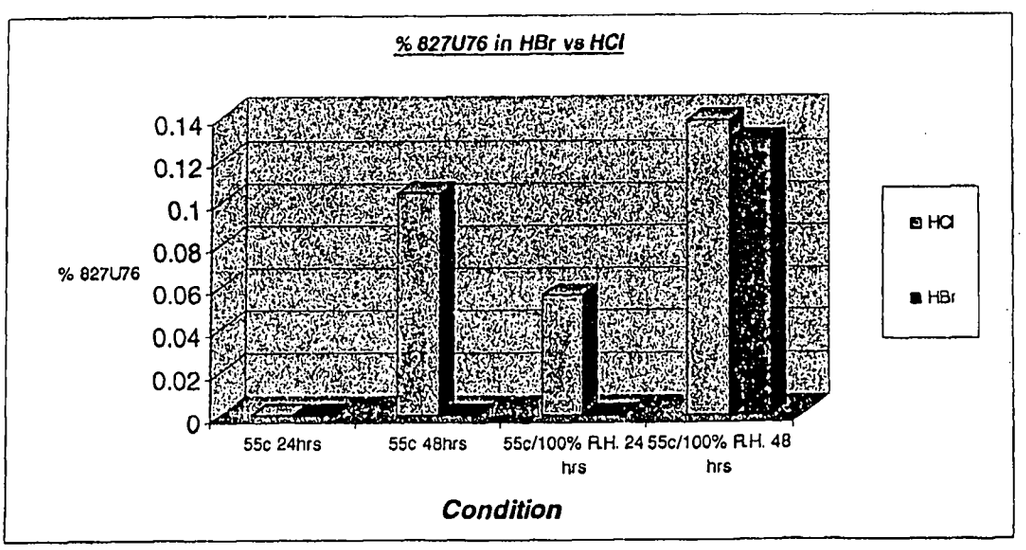
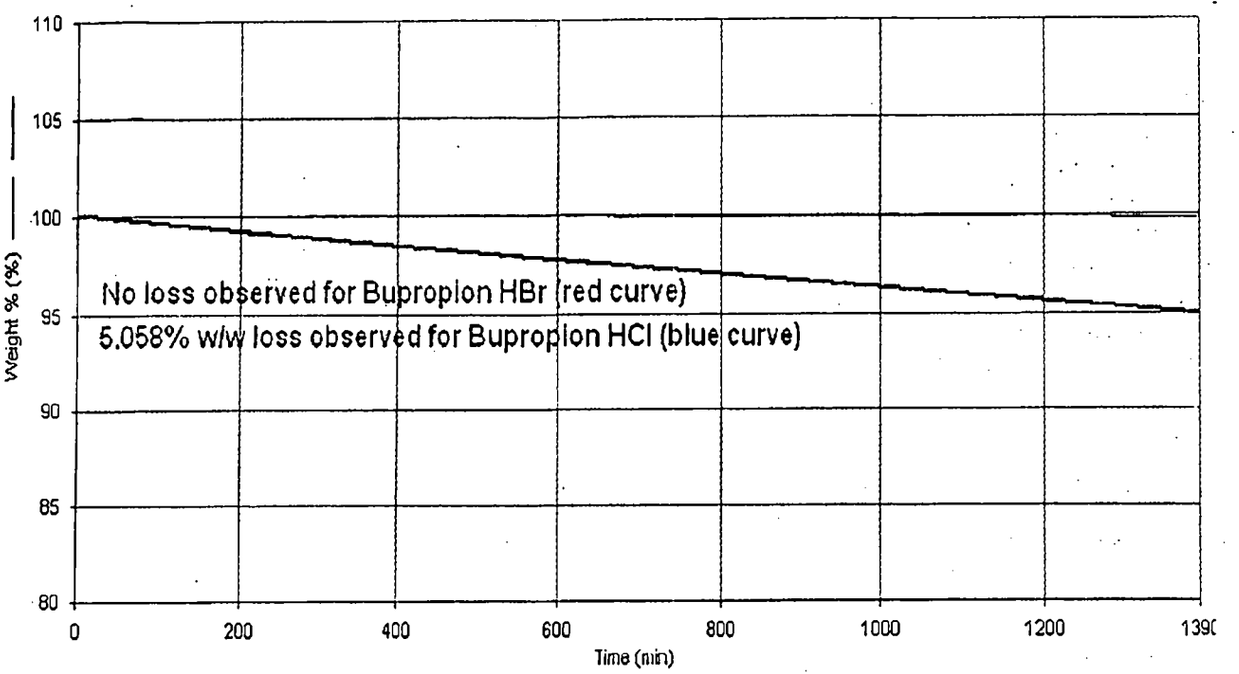

% 827U76 in HBr vs HCl
0.14
0.12
0.1
0.08
% 827U76
0.06
0.04
0.02
0
55c 24hrs
55c 48hrs
55c/100% R.H. 24 hrs
55c/100% R.H. 48 hrs
Condition
HCl
HBr

Figure 53


110
105
100
95
90
85
80
Weight % (%)
No loss observed for Bupropion HBr (red curve)
5.058% w/w loss observed for Bupropion HCl (blue curve)
0
200
400
600
800
1000
1200
Time (min)

CONFIDENTIAL INFORMATION

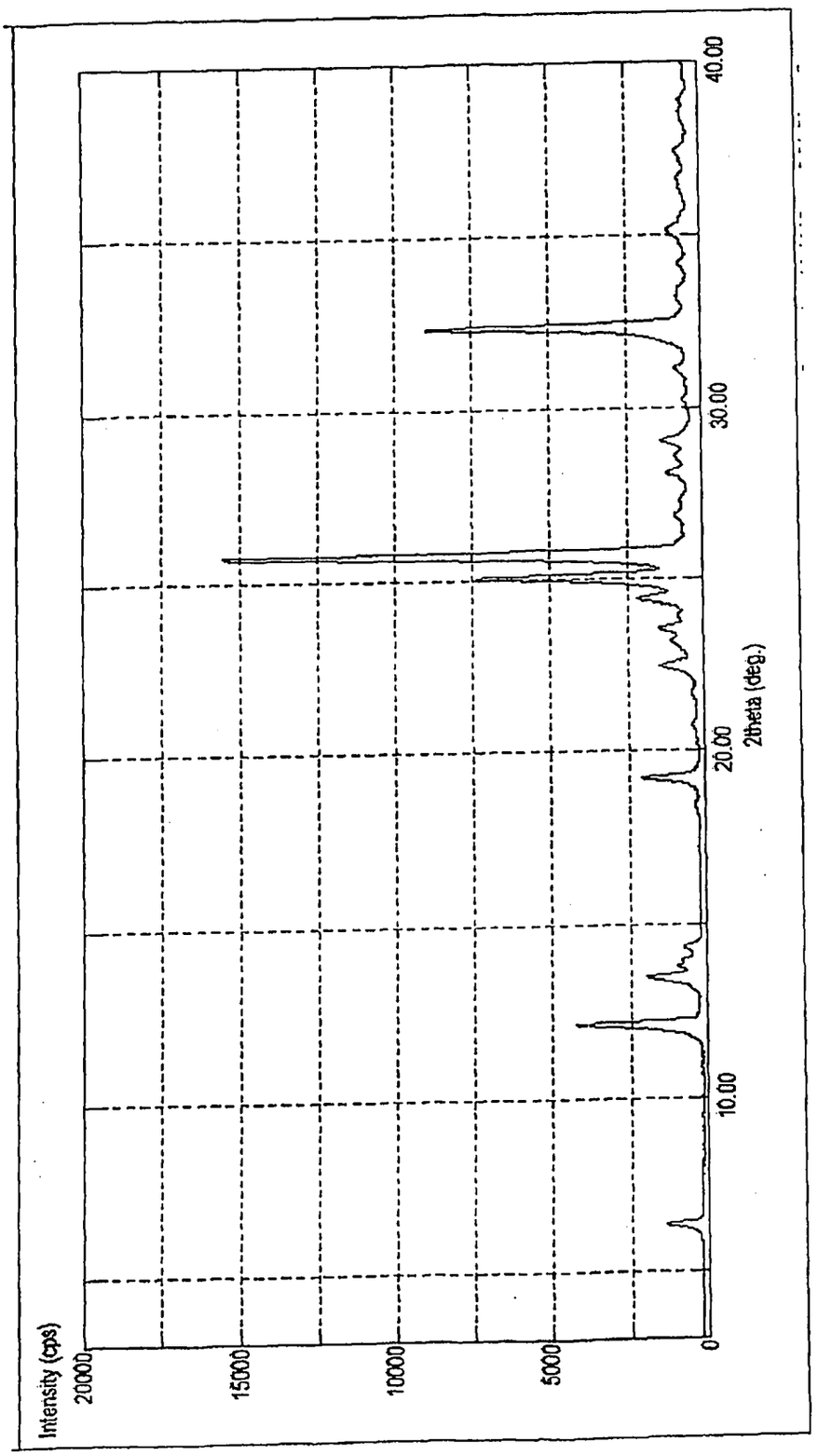


Figure 54

PXRD of Bupropion Hydrobromide Polymorphic Form I

CONFIDENTIAL INFORMATION

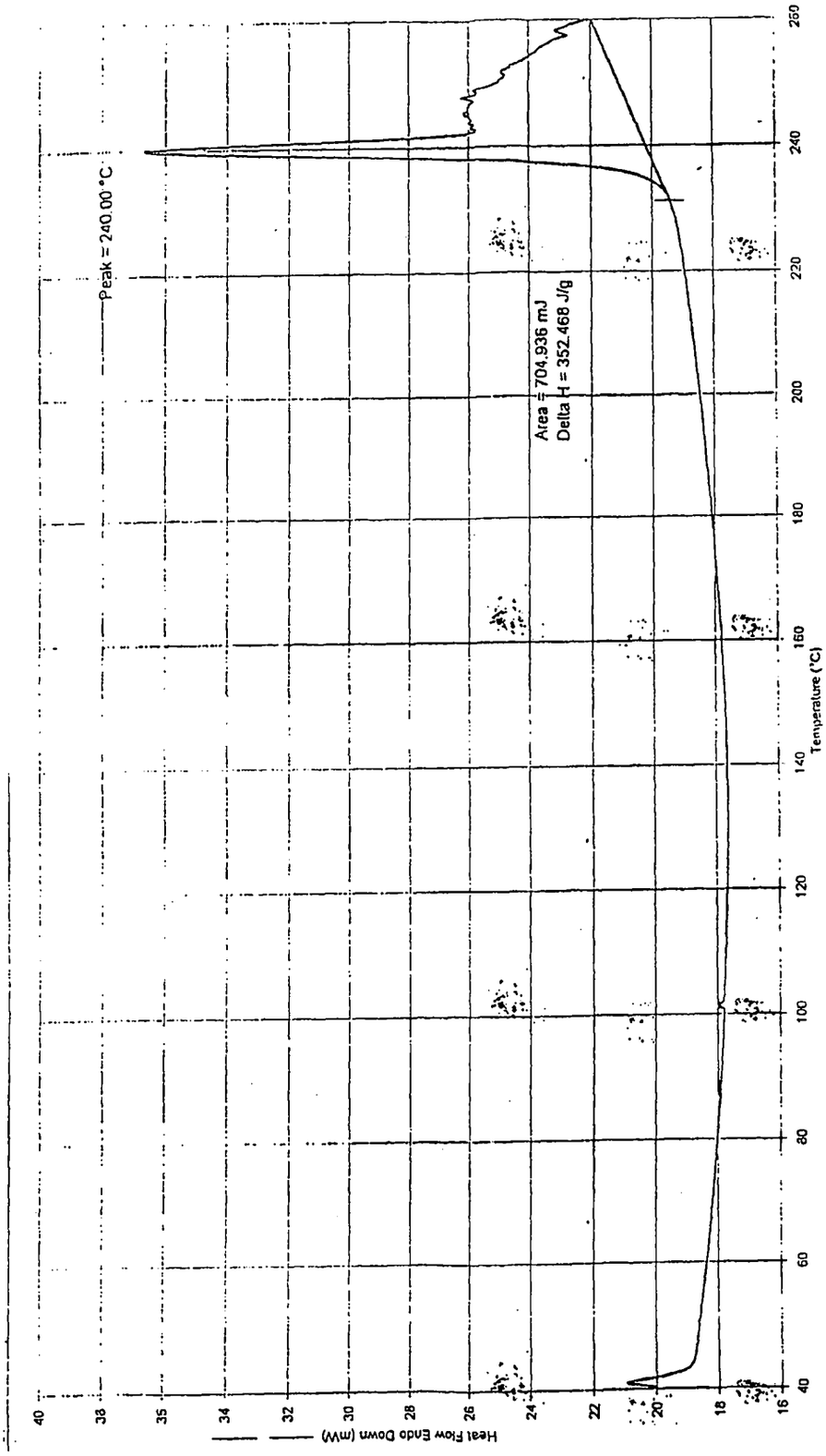


Figure 55
DSC of Bupropion Hydrobromide Polymorphic Form I

CONFIDENTIAL INFORMATION

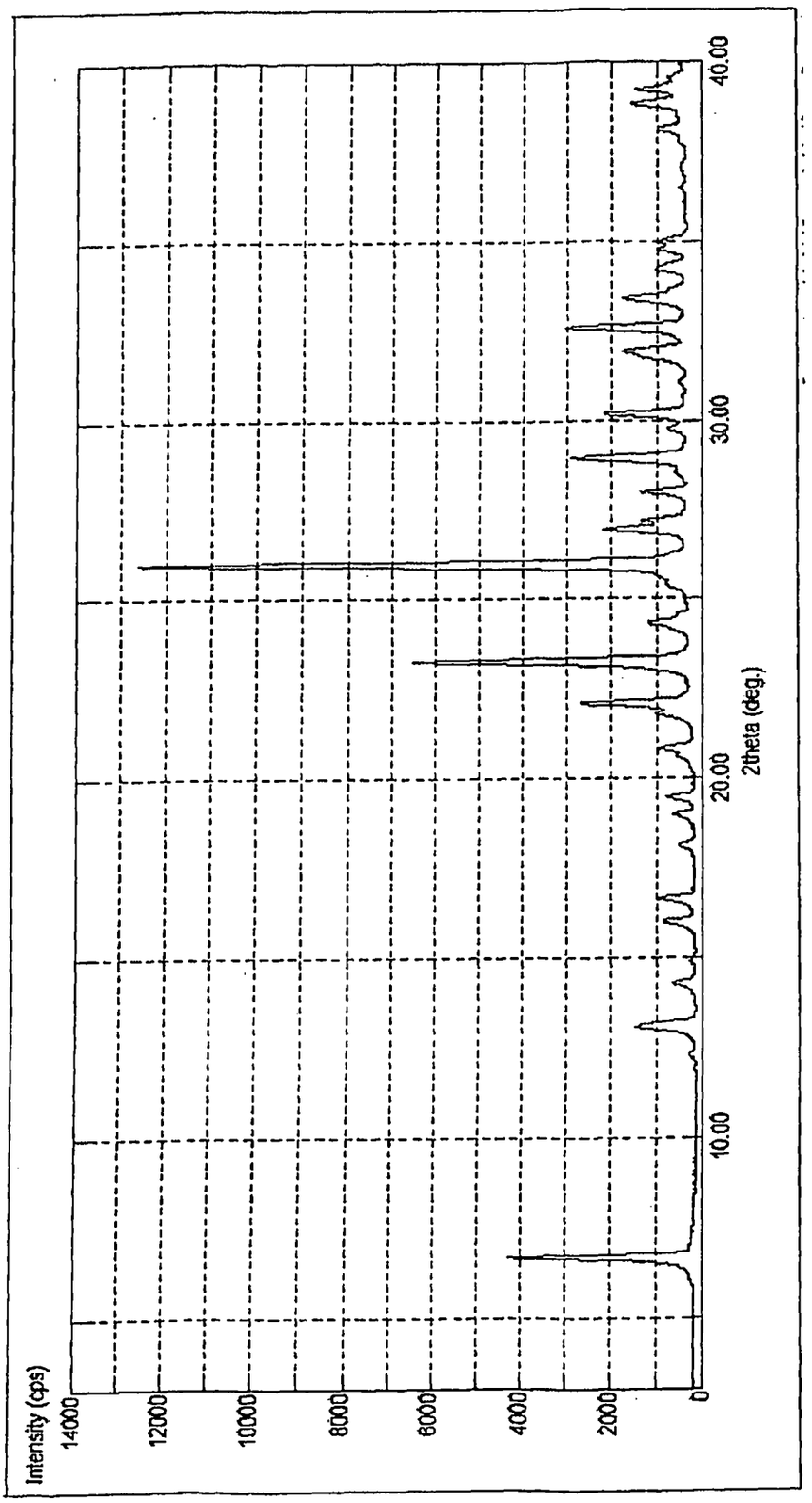


Figure 56
PXRD of Bupropion Hydrobromide Polymorphic Form II

CONFIDENTIAL INFORMATION

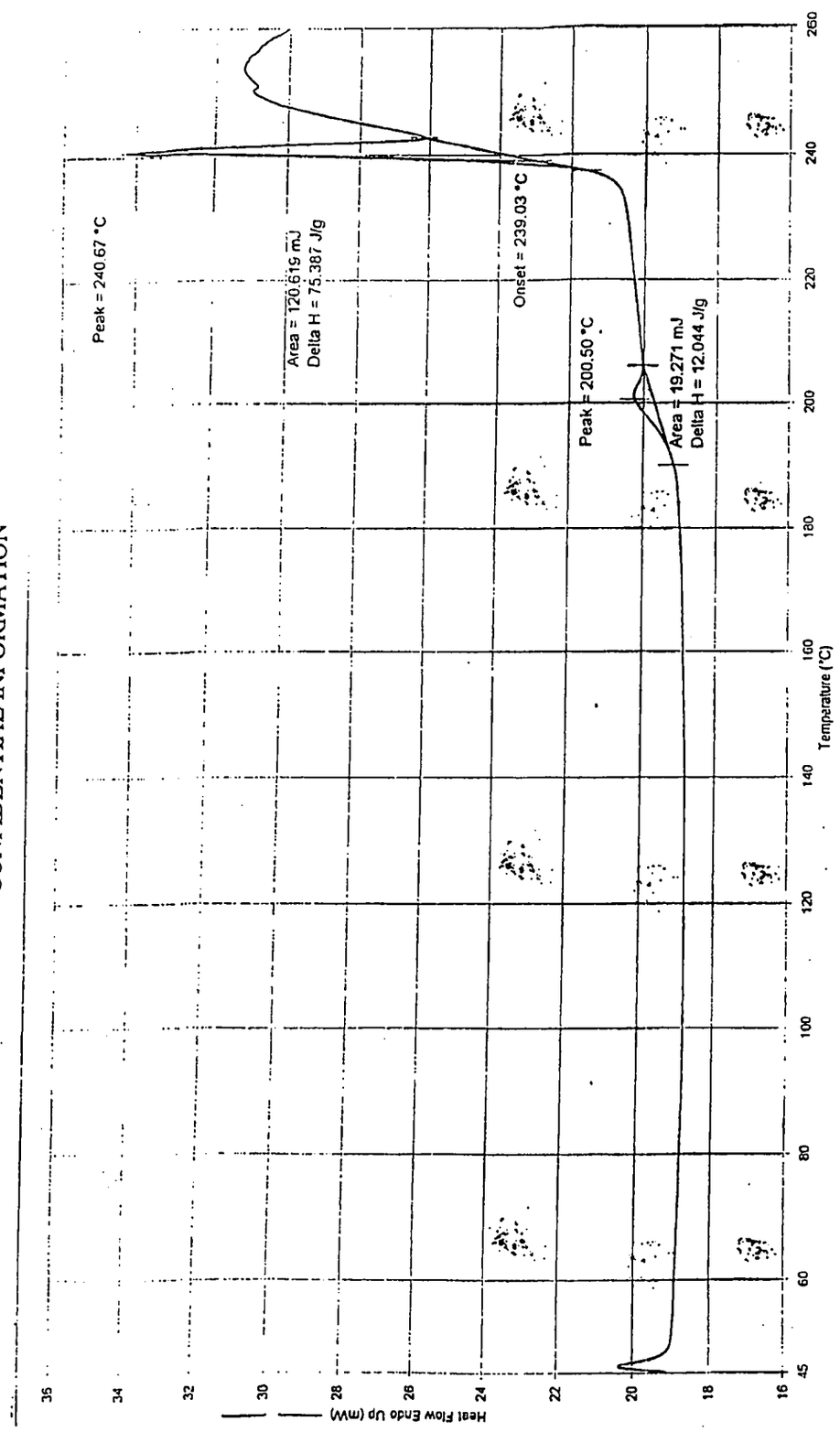


Figure 57
DSC of Bupropion Hydrobromide Polymorphic Form II

CONFIDENTIAL INFORMATION

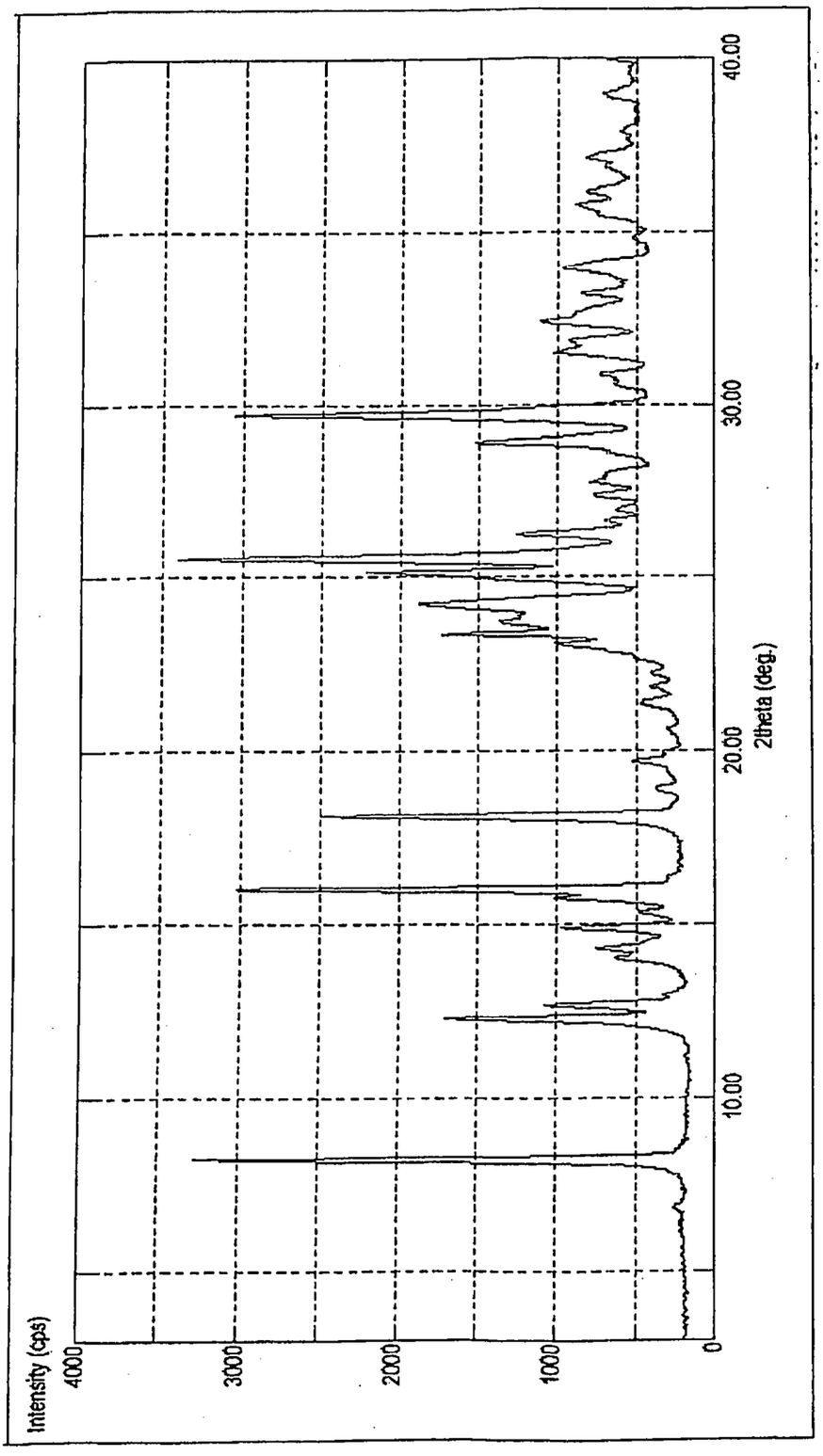


Figure 58
PXRD of Bupropion Hydrobromide Polymorphic Form III

CONFIDENTIAL INFORMATION

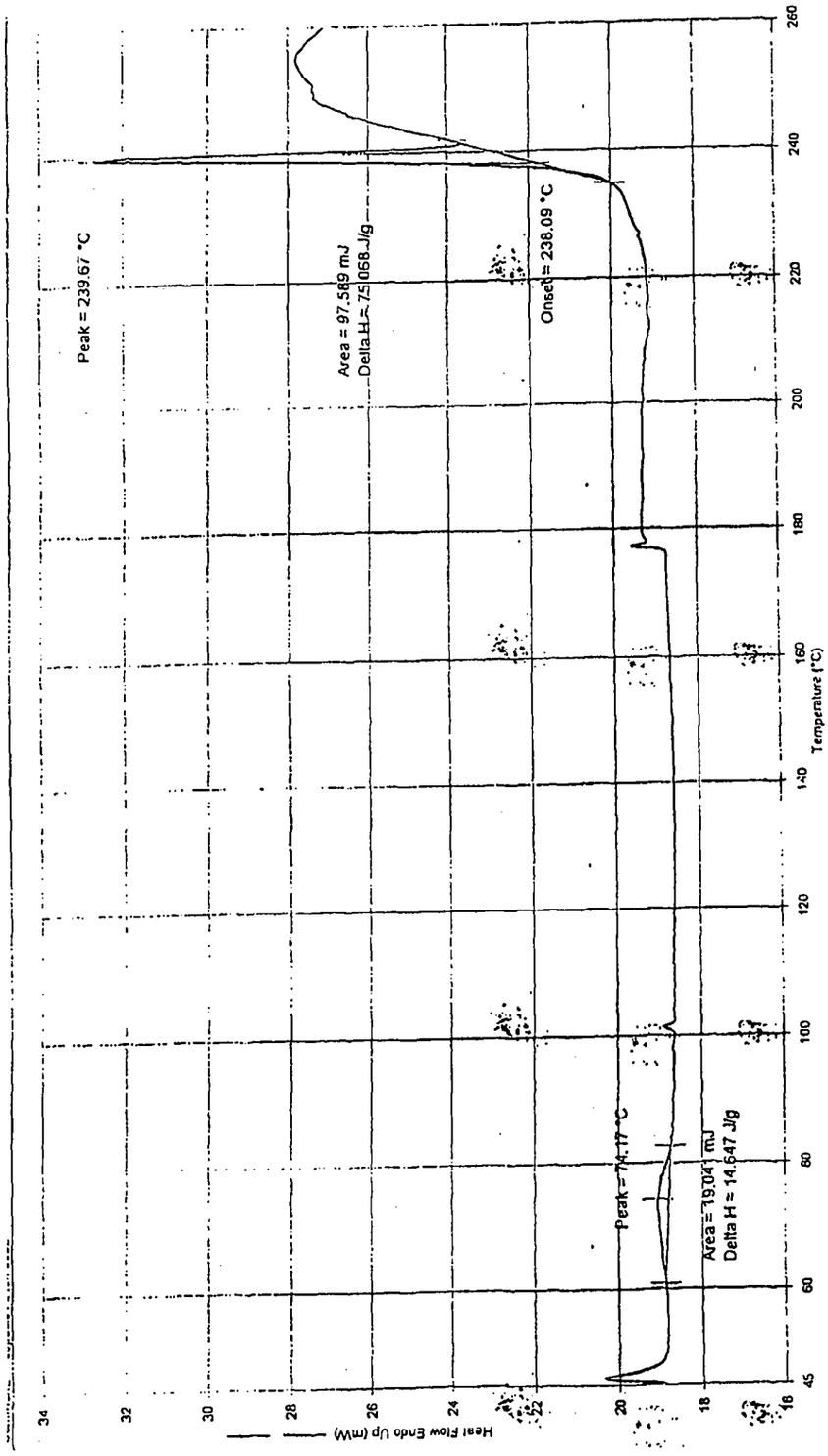


Figure 59
DSC of Bupropion Hydrobromide Polymorphic Form III

CONFIDENTIAL INFORMATION

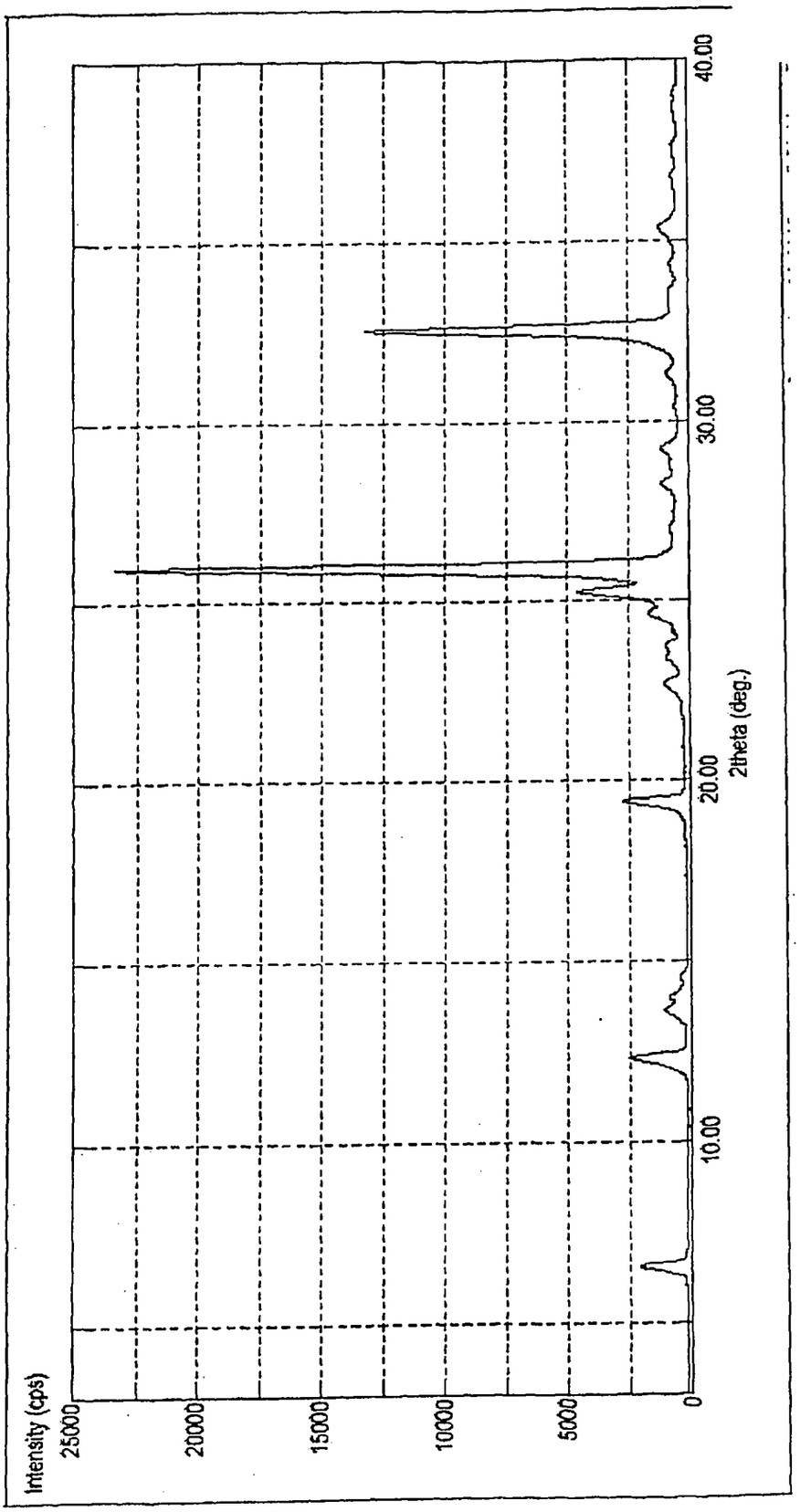


Figure 60
PXRD of Bupropion Hydrobromide Form I after 6 months in ICH Conditions (40°C, 75% R.H.)

CONFIDENTIAL INFORMATION

Chemi SpA

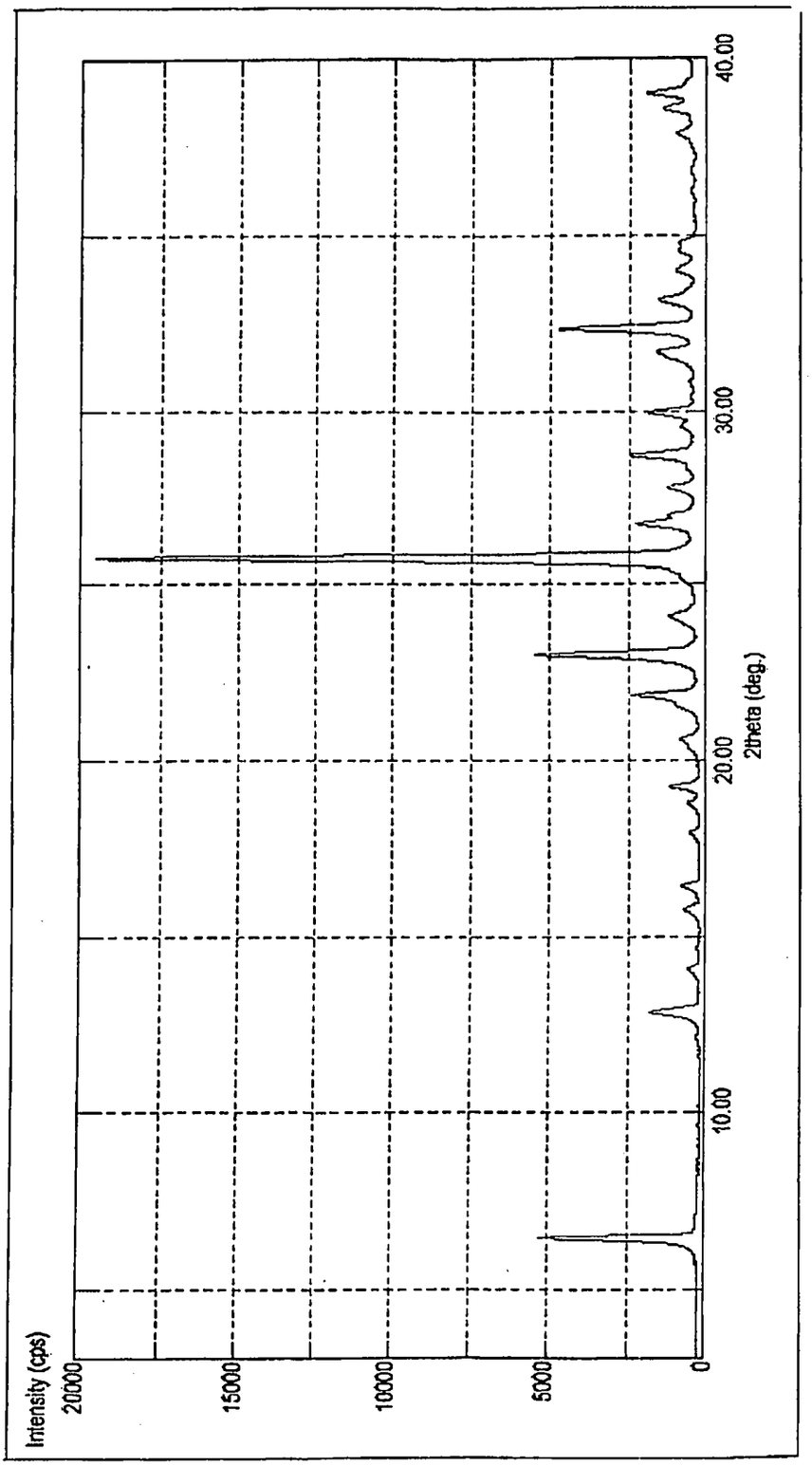


Figure 61
PXRD of Bupropion Hydrobromide Polymorphic Form II after 1 month in ICH Conditions (40°C, 75% R.H.)

CONFIDENTIAL INFORMATION

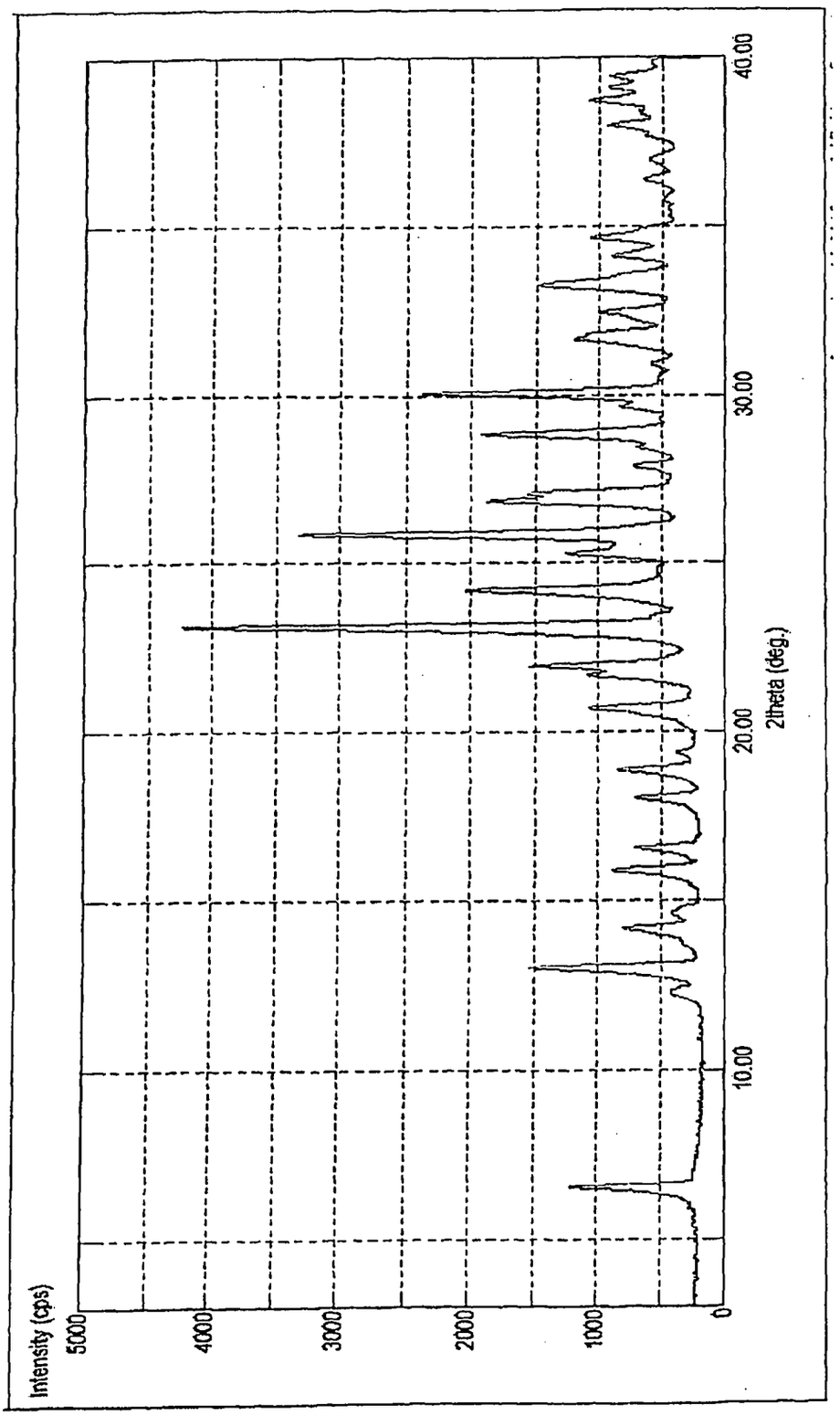


Figure 62
PXRD of Bupropion Hydrobromide Polymorphic Form III after 1 month in ICH Conditions (40°C, 75% R.H.)

Chemi SpA

INTERIM STABILITY REPORT

roject: BUP 10121		Product: ***Bupropion HBr XL Tablets 348mg***				Lot No.: ***Bup-HBr-XL-348-025-5*** Expiry Date: N/A	
ctive Drug Mfg Site:	N/A	Product Mfg Site: N/A	Packg. Site: N/A		Packg. Date: N/A	Stability Study # :	STAB-05/064
ctive Drug Mfg Date:	N/A	Product Mfg Date: N/A	Container: Bottle		Desiccant: N/A	Stability Program:	Long term
ctive Drug Lot #:	N/A	Product Batch Size: N/A	Closure: N/A		Count: 90's	Storage Condifions:	25°C/60%RH
ctive Drug Expiry Date:	N/A	Product Description: N/A				Schedule:	Initial, 3M, 6M, 9M, 12M

TEST & METHODS	SPECIFICATIONS	INITIAL	3 MONTHS	6 MONTHS	9 MONTHS	12 MONTHS
		Date: May 20/05	Date: Aug 20/05	Date: Nov 20/05	Date: Feb 20/06	Date: May 20/06
	Lab Sample #	E05-71	H05-35	K05-51	B06-51	
Description	Report Results	Off-white colour, round tablets	Conforms	Conforms	Conforms	
Assay (%)	Report Results	99.6	99.4	97.4	96.8	
Impurities (%)						
3-CBA	NMT 0.7%	0.012	0.046	0.071	0.172	
852U77	NMT 1.0%	0.028	0.138	0.185	0.207	
20U78/diluent	NMT 0.3%	0.034	0.051	0.040	0.046	
827U76	NMT 0.4%	ND	0.011	0.018	0.010	
Major Unknown	Report Results	0.253 (RRT 0.14)	0.186 (RRT 0.13)	0.657 (RRT 0.09)	0.177 (RRT 0.15)	
Toral Unknown	Report Results	0.376	0.342	1.055	0.280	
Total Impurities	Report Results	0.45	0.59	1.37	0.72	
KF (%)	Report Results	0.62	0.85	0.42	0.49	
Dissolution*						
2H	NMT 20%	14 - 19 (16)	13 - 17 (15)	12 - 17 (14)	12 - 20 (16)	-
4H	20 - 45%	33 - 40 (36)	30 - 35 (32)	29 - 36 (32)	29 - 40 (34)	-
8H	65 - 85%	64 - 72 (68)	57 - 64 (61)	54 - 63 (58)	55 - 68 (61)	-
16H	NLT 80%	92 - 101 (98)	91 - 98 (94)	89 - 97 (93)	92 - 100 (96)	-

*Tentative specification

Reviewed by / Date:

INTERIM STABILITY REPORT

Project: BUP 10121		Product: ***Bupropion HBr EA Tablets 300mg***				Lot No.:	***Bup-HBr-EA-300-00T-5***
						Expiry Date:	N/A
Active Drug Mfg Site:	N/A	Product Mfg Site: N/A	Packg. Site:	N/A	Packg. Date: N/A	Stability Study # :	STAB-05/072
Active Drug Mfg Date:	N/A	Product Mfg Date: Apr 19/05	Container:	Bottle	Desiccant: N/A	Stability Program:	Accelerated
Active Drug Lot #:	N/A	Product Batch Size: N/A	Closure:	N/A	Count: 90 counts	Storage Conditions:	40°C/75%RH
Active Drug Expiry Date:	N/A	Product Description: Coated Tablets - 54mg Wt gain				Schedule:	Initial, 1M, 2M, 3M, 6M

TEST & METHODS	SPECIFICATIONS	INITIAL	1 MONTH	2 MONTHS	3 MONTHS	6 MONTHS
		Date: Jun 13/05	Date: Jul 13/05	Date: Aug 13/05	Date: Sep 13/05	Date: Dec 13/05
	Lab Sample #	F05-5	G05-10	H05-24	I05-13	L05-23
Description	Report Results		Conforms	Conforms	Conforms	Conforms
Assay (%)	Report Results	102.3	99.6	98.0 (*)	101.8	101.0
Impurities (%)						
3-CBA	NMT 0.7%	0.017	0.052	0.180	0.170	0.318
852U77	NMT 1.0%	0.023	0.221	0.438	0.256	0.221
20U78/diluent	NMT 0.3%	0.044	0.036	0.032	0.057	0.059
827U76	NMT 0.4%	0.013	0.043	0.032	0.030	0.037
Major Unknown	Report Results	0.623 (RRT 0.10)	0.315 (RRT 0.10)	0.205 (RRT 0.13)	0.245 (RRT 0.14)	0.651 (RRT 0.10)
Total Unknown	Report Results	1.054	0.675	0.381	0.421	1.125
Total Impurities	Report Results	1.15	1.03	1.06	0.93	1.76
KF (%)	Report Results	1.02	0.81	1.39	0.79	0.42
Dissolution*						
2H	NMT 20%	13 - 15 (14)	14 - 17 (16)	15 - 17 (16)	14 - 18 (16)	12 - 13 (13)
4H	20 - 45%	32 - 35 (33)	33 - 37 (35)	35 - 38 (36)	33 - 38 (35)	28 - 31 (30)
8H	65 - 85%	64 - 69 (66)	64 - 69 (67)	65 - 71 (68)	62 - 68 (65)	55 - 59 (57)
16H	NLT 80%	96 - 101 (98)	97 - 100 (98)	97 - 102 (99)	95 - 99 (97)	90 - 92 (91)

*Tentative specification

Comments: Note: Impurity results calculated based on ***correct values***

Reviewed by / Date:

WO 2007/002597
PCT/US2006/024832

INTERIM STABILITY REPORT

Project: BUP 10121		Product: ***Bupropion HBr EA Tablets 300mg***					Lot No.: ***Bup-HBr-EA-300-001-5*** Expiry Date: N/A
Active Drug Mfg Site:	N/A	Product Mfg Site: N/A	Packg. Site:	N/A	Packg. Date:	N/A	Stability Study # : STAB-05/072
Active Drug Mfg Date:	N/A	Product Mfg Date: Apr 19/05	Container:	Bottle	Desiccant:	N/A	Stability Program: Accelerated
Active Drug Lot #:	N/A	Product Batch Size: N/A	Closure:	N/A	Count:	90 counts	Storage Conditions: 40°C/75%RH
Active Drug Expiry Date:	N/A	Product Description: Coated Tablets - 54mg Wt gain					Schedule: Initial, 1M, 2M, 3M, 6M
							Approved by / Date:

Bupropion HBr XL 174mg core, Lot# Bup-HBr-XL-004-5 core

Tests	Initial	Open-Closed bottle stability (40C/75% RH)			
		10 Days-Open	10Days -Closed	20 Days-Open	20Days-Closed
%Assay	100.1	98.7	98.2	99.2	97.6
%Impurities					
3-CBZ	0.010	0.179	0.184	0.276	0.465
852U77	0.019	0.209	0.268	0.248	0.416
20U78/dilu	0.054	0.055	0.060	0.058	0.063
827U76	0.026	0.131	0.308	0.102	0.497
Total unknown	0.054	0.043	0.075	0.042	0.038
Total	**016**	**0.62**	**0.89**	**0.73**	**1.48**

Bupropion HBr XL 348mg core , Lot# Bup-HBr-XL-009-5 core

Tests	Initial	Open-Closed bottle stability (40C/75% RH)			
		10 Days-Open	10Days -Closed	20 Days-Open	20Days-Closed
%Assay	98.3	97.8	95.6	96.9	98.0
%Impurities					
3-CBZ	0.016	0.106	0.121	0.146	0.166
852U77	0.091	0.391	0.411	0.414	0.483
20U78/dilu	0.054	0.051	0.055	0.056	0.055
827U76	0.020	0.077	0.102	0.059	0.119
Total unknown	0.053	0.126	0.156	0.124	0.142
Total	**0.23^**	**0.74**	**0.84**	**0.80**	**0.97**

Bupropion HCl XL 150mg core , Lot# 05E056

Tests	Initial	Open-Closed bottle stability (40C/75% RH)			
		10 Days-Open	10Days -Closed	20 Days-Open	20Days-Closed
%Assay	97.5	98.4	97.5	98.1	97.6
%Impurities					
3-CBZ	0.006	0.079	0.052	0.185	0.238
852U77	0.043	0.406	0.342	0.520	0.685
20U78/dilu	0.044	0.046	0.046	0.059	0.052
827U76	0.028	0.050	0.074	0.069	0.127
Total unknown	0.058	0.051	0.066	0.044	0.040
Total	**0.18**	**0.63**	**0.58**	**0.88**	**1.14**

Bupropion HCl XL 300mg core , Lot# 05D380

Tests	Initial	Open-Closed bottle stability (40C/75% RH)			
		10 Days-Open	10Days -Closed	20 Days-Open	20Days-Closed
%Assay	99.2	99.1	98.4	96.8	97.1
%Impurities					
3-CBZ	0.006	0.100	0.016	0.245	0.171
852U77	0.037	0.409	0.274	0.564	0.515
20U78/dilu	0.044	0.045	0.046	0.051	0.050
827U76	0.015	0.058	0.039	0.099	0.105
Total unknown	0.044	0.038	0.045	0.032	0.052
Total	**0.15**	**0.65**	**0.42**	**0.99**	**0.90**

Bup-Stab-HBr-XL174 -150- 300-348 core-study-2b

Bupropion HBr XL 348mg tablets (final) -Lot# Bup-HBr-XL-012-5 (USP3)

Medium/Time Points	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	***Mean***
SGF pH 1.2 2hrs	9.0	8.3	8.9	11.6	8.8	8.6	***9.2***
Acetate buffer pH 4.5 2hrs	15.8	15.0	19.3	18.5	17.5	18.2	***17.4***
Phospate buffer SIF pH 6.8 2hrs	26.8	25.4	24.9	33.3	27.7	24.2	***27.1***
2hr	24.2	15.5	24.8	31.9	37.8	15.3	***24.9***
2hrs	22.5	19.5	16.6	1.4	2.4	25.8	***14.7***
6hrs	1.0	11.6	0.8	0.2	0.2	6.1	***3.3***
Total %Released	99.3	95.3	95.3	96.9	94.4	98.2	***96.6***

Wellbutrin XL 300mg tablets (final) -Lot# 05A116 (USP3)

Medium/Time Points	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	***Mean***
SGF pH 1.2 2hrs	3.1	2.7	2.1	1.8	2.8	2.6	***2.5***
Acetate buffer pH 4.5 2hrs	53.0	38.8	32.6	10.7	20.1	38.8	***32.3***
Phospate buffer SIF pH 6.8 2hrs	30.8	36.4	37.0	47.8	46.1	33.5	***38.6***
2hr	5.6	15.2	25.0	22.4	22.8	19.6	***18.4***
2hrs	2.2	3.1	1.6	13.7	2.8	0.8	***4.0***
6hrs	0.9	0.3	0.2	0.9	0.2	0.1	***0.4***
Total %Released	95.7	96.3	98.4	97.3	94.8	95.2	***96.3***

Bupropion HBr XL 348mg tablets ECI) -Lot# Bup-HBr-XL-012-5 (EC 32mg wg.) (USP3)

Medium/Time Points	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	***Mean***
SGF pH 1.2 2hrs	47.6	45.7	45.0	51.3	42.7	48.0	***46.7***
Acetate buffer pH 4.5 2hrs	38.0	37.9	37.3	37.9	36.0	38.0	***37.5***
Phospate buffer SIF pH 6.8 2hrs	13.0	13.9	16.0	10.3	15.8	12.3	***13.5***
2hr	1.9	2.1	3.1	0.9	3.5	1.5	***2.2***
2hrs	0.4	0.5	0.9	0.2	1.0	0.3	***0.6***
6hrs	0.2	0.2	0.4	0.1	0.4	0.1	***0.2***
Total %Released	100.9	100.3	102.7	100.6	99.4	100.2	***100.7***

Wellbutrin XL 300mg tablets (ECI) -Lot# 05D047 (USP3)

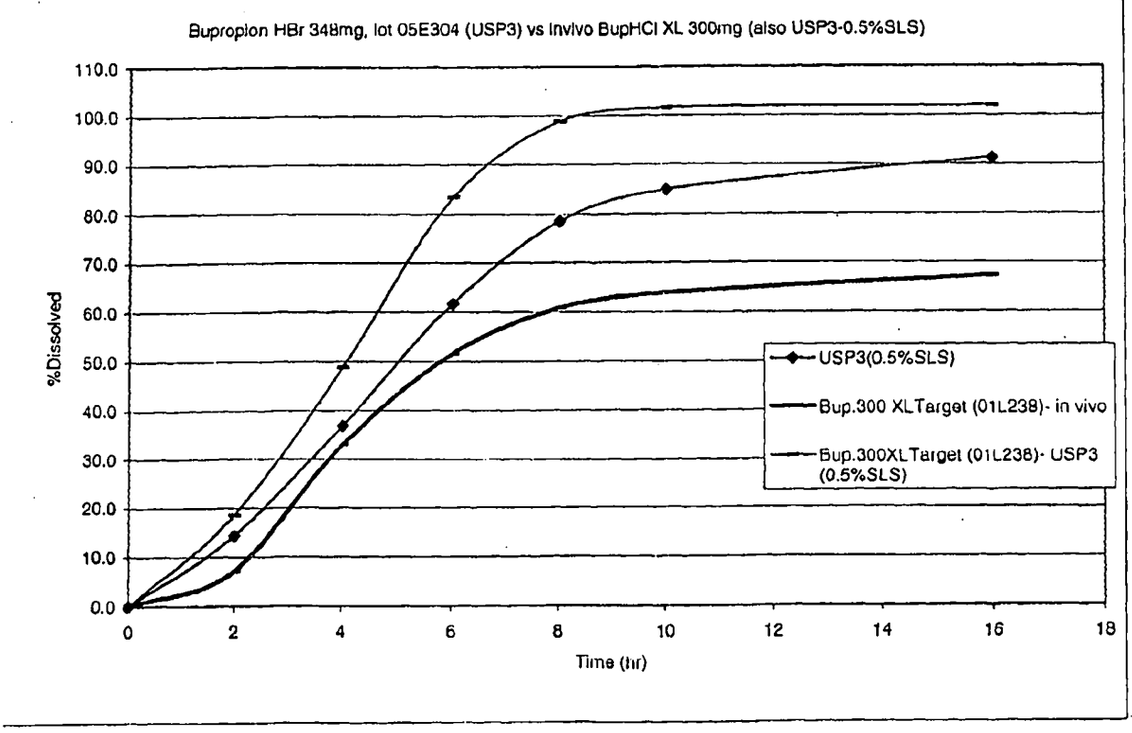
Medium/Time Points	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	***Mean***
SGF pH 1.2 2hrs	63.1	61.5	58.9	58.2	57.9	60.8	***60.1***
Acetate buffer pH 4.5 2hrs	32.9	35.4	36.6	38.2	37.2	35.3	***35.9***
Phospate buffer SIF pH 6.8 2hrs	0.6	0.9	1.0	1.0	1.1	0.9	***0.9***
2hr	0.0	0.1	0.1	0.1	0.1	0.1	***0.1***
2hrs	0.0	0.0	0.0	0.0	0.0	0.0	***0.0***
6hrs	0.0	0.1	0.1	0.0	0.1	0.0	***0.0***
Total %Released	96.7	97.9	96.6	97.6	96.3	97.1	***97.0***

BupHBr-348mg-WXL 300- EC and final coat-USP3

SP-3 Different media (SGF pH 1.2+0.5%SLS, Acetate buffer pH 4.5 & Phosphate buffer pH 6.8) upropion HBr 348mg Lot 05E304

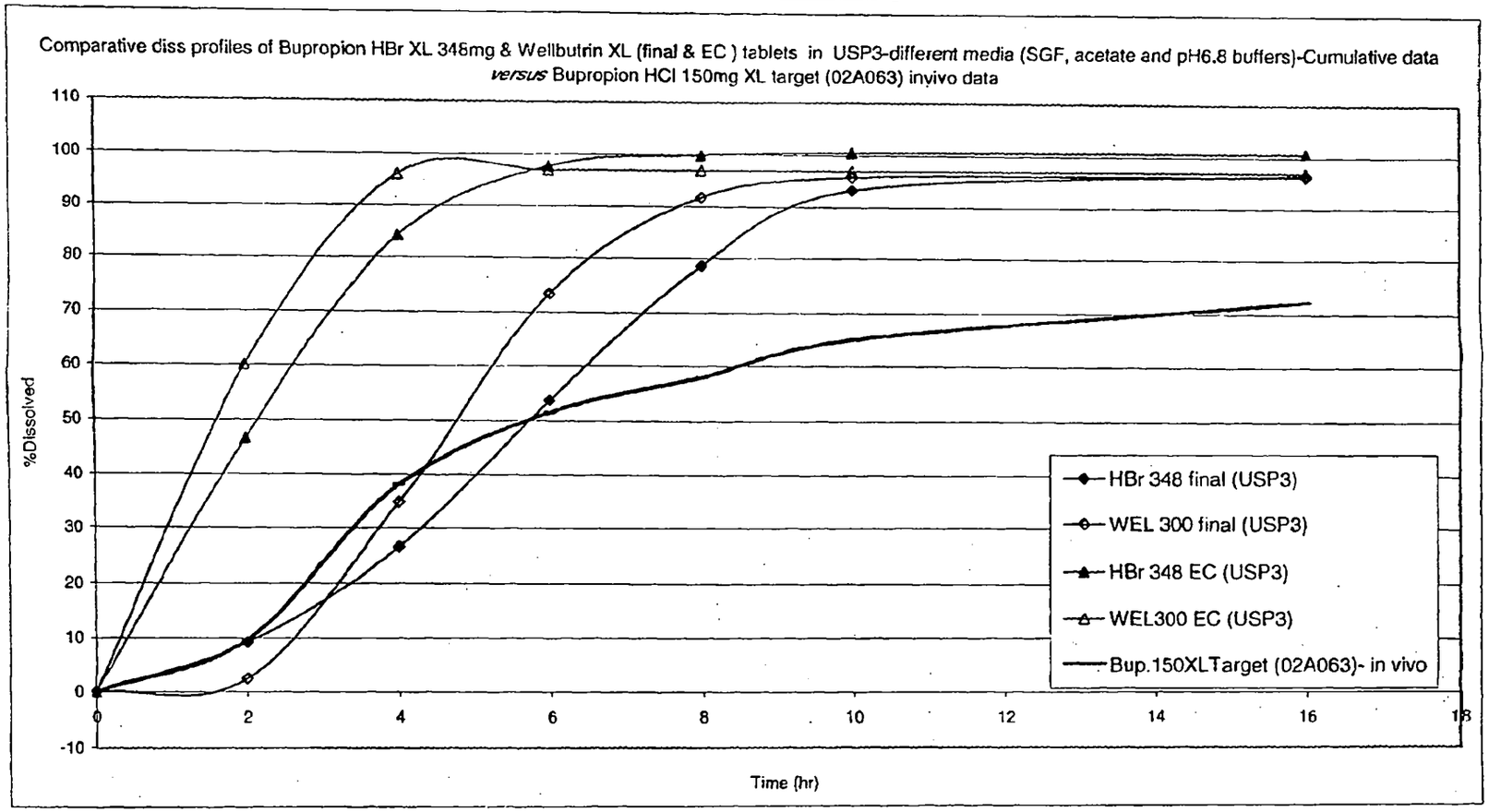
Medium/Time Points	Vessel-1	Vessel-2	Vessel-3	Vessel-4	Vessel-5	Vessel-6	Mean
SF pH 1.2 + 0.5%SLS 2hrs	14.5	14.6	12.5	14.9	13.3	16.3	**14.3**
cetate buffer pH 4.5 2hrs	23.2	21.7	19.6	23.1	22.2	26.0	**22.6**
hosphate buffer SIF pH 6.8 2hrs	26.1	25.1	23.9	24.7	25.3	23.6	**24.8**
2hr	16.1	20.7	16.5	14.3	16.7	16.3	**16.8**
2hrs	12.9	15.2	9.4	10.2	10.4	10.6	**11.4**
6hrs	2.5	1.1	2.6	14.4	11.3	6.8	**6.4**
otal %Released	95.3	98.2	84.5	101.6	99.1	99.5	**96.4**

Time (hrs)	SP3(0.5%SLS	Bup.300 XLTarget (01L238)- in vivo	Bup.300XLTarget (01L238)- USP3 (0.5%SLS)			
0	0.0	0.0	0.0			
2	14.3	7.1	18.5			
4	36.9	30.0	48.8			
6	61.7	54.5	83.4			
8	78.5	66.8	98.9			
10	84.9	69.8	101.5			
16	91.3	67.2	101.9			



Cumulative data
(USP3- SGF pH1.2, Acbuffer pH4.5, Phosp. Buffer pH 6.8)

Time (hrs)	HBr 348 final (USP3)	WEL 300 final (USP3)	HBr 348 EC (USP3)	WEL300 EC (USP3)	Bup.150XLTarget (02A063)- *in vivo*
0	0.0	0.0	0.0	0.0	0.0
2	9.2	2.5	46.7	60.1	9.7
4	26.6	34.8	84.2	96.0	38.1
6	53.7	73.4	97.7	96.9	51.5
8	78.6	91.8	99.9	97.0	58.0
10	93.3	95.8	100.5	97.0	65.0
16	96.6	96.2	100.7	97.0	72.3



BupHBr-348mg-WXL 300- EC and final coat-USP3

FORMULACIONES DE UNA SAL DE BUPROPION DE LIBERACIÓN MODIFICADA

APLICACIONES RELACIONADAS

La presente solicitud reivindica prioridad frente a la solicitud provisional de los Estados Unidos 60/693,906 presentada el 27 de junio de 2005, el contenido de la cual se incorpora por referencia en su totalidad.

CAMPO DE LA INVENCIÓN

Existe la necesidad de formas farmacéuticas que comprendan una sal farmacéuticamente aceptable de bupropion que sea más estable que el clorhidrato de bupropion. En consecuencia, la presente invención se relaciona con formas farmacéuticas que comprenden una cantidad eficaz de una sal farmacéuticamente aceptable de bupropion que es más estable que el clorhidrato de bupropion. La presente invención también se relaciona con el uso de dichas formas farmacéuticas para el tratamiento en un sujeto de una o más afecciones adecuadas para el tratamiento mediante bupropion o sus sales farmacéuticamente aceptables como la depresión, la adicción a la nicotina y la obesidad.

ANTECEDENTES

El bupropion es un antidepresivo que no está relacionado químicamente con los inhibidores selectivos de la recaptación de serotonina (ISRS) tricíclicos o tetracíclicos ni con otros agentes antidepresivos conocidos. El fármaco se asemeja a un psicoestimulante en cuanto a sus perfiles neuroquímicos y de comportamiento in vivo, pero no produce efectos confiables similares a los estimulantes en los seres humanos a las dosis prescritas clínicamente. Su estructura se asemeja estrechamente a la del dietilpropion y está relacionado con feniletilaminas. Se designa como clorhidrato de (±)-1-(3-clorofenil)-2-[(1,1-dimetiletil)amino]-1-propanona y por su nombre genérico clorhidrato de anfebutamona. El clorhidrato de bupropion se comercializa como una forma de liberación inmediata (Wellbutrin®) y como una forma de liberación sostenida (Wellbutrin® SR y Zyban®). Tanto Wellbutrin® SR como Zyban® son química y farmacéuticamente idénticos.

El mecanismo neuroquímico del efecto antidepresivo del bupropion no se conoce bien. El bupropion no inhibe la monoaminooxidasa. El bupropion afecta a los productos químicos dentro del cerebro que los nervios usan para enviarse mensajes entre sí. Estos mensajeros químicos se llaman neurotransmisores. Los neurotransmisores que son liberados por los nervios son retomados por los nervios que los liberan para su reutilización (esto se denomina recaptación). Muchos expertos creen que la depresión es causada por un desajuste entre las cantidades de neurotransmisores que se liberan. Se cree que el bupropion actúa inhibiendo la recaptación de los neurotransmisores dopamina, serotonina y norepinefrina, una acción que da lugar a que haya más dopamina, serotonina y norepinefrina disponibles para transmitir mensajes a otros nervios. En consecuencia, el bupropion es único en que su efecto principal es sobre la dopamina, un efecto que no es compartido por los ISRS (por ejemplo, la paroxetina (Paxil®), la fluoxetina (Prozac®), la sertralina (Zoloft®)) ni los antidepresivos tricíclicos o ATC (por ejemplo, la amitriptilina (Elavil®), la imipramina (Tofranil®), y la desipramina (Norpramin®)).

Wellbutrin® y Wellbutrin® SR se usan para el tratamiento de la depresión. Zyban® se aprobó como una ayuda para los pacientes que quieren dejar de fumar. Wellbutrin®, la formulación de bupropion de liberación inmediata, se administra tres veces al día, adecuadamente con 6 o más horas entre las dosis. Para los pacientes que requieren más de 300 mg de bupropion por día, cada dosis no debe exceder de 150 mg. Esto requiere una administración de los comprimidos al menos 4 veces al día con al menos 4 horas entre las dosis. La formulación de liberación inmediata da lugar a más de un 75 % de liberación de bupropion en el medio de disolución en 45 minutos y uno de los efectos colaterales graves del bupropion ha sido la incidencia de crisis convulsivas, que en parte parece estar muy asociado con la liberación inmediata de bupropion en el sistema. En consecuencia, se desarrollaron productos de liberación sostenida para evitar la incidencia de crisis convulsivas. Los productos de liberación sostenida se administran dos veces al día.

En general, el cumplimiento del paciente es un problema con los medicamentos que requieren un régimen de dosificación múltiple y es especialmente problemático en individuos deprimidos. Si bien las formulaciones de liberación sostenida simplificaron el régimen de dosificación y aumentaron el cumplimiento del paciente, todavía hay espacio para simplificar aún más el régimen de dosificación y la adherencia del paciente a dicho régimen de dosificación. El desarrollo de una formulación estable aprobada de bupropion, para administrar una vez al día y de liberación modificada sería un adelanto en el área.

La selección de una sal adecuada para un fármaco candidato es un paso importante en la fase preclínica del desarrollo de fármacos; sin embargo, la bibliografía científica sobre este tema es bastante limitada. Cambiar la forma salina de un fármaco es un medio reconocido de modificar sus propiedades químicas y biológicas sin modificar su estructura. Hasta ahora, no hay manera fiable de predecir exactamente qué efecto tendrá cambiar la forma salina de un fármaco activo sobre su actividad biológica. La decisión de cambiar la forma salina en una etapa posterior introduce la necesidad de repetir las pruebas toxicológicas, de formulación y estabilidad, con las implicaciones obvias para el desarrollo general y tiempo de producción para el nuevo producto farmacéutico.

En general, unos pocos factores que deben considerarse durante la selección de una sal incluyen: ¿Cuál es el efecto de la sal sobre la estabilidad química del principio activo y del producto farmacéutico? ¿Forma la sal un hidrato? ¿Cuál es la solubilidad de la sal y si es apropiada para la administración in vivo? ¿Cuál es la calidad de la sal con respecto al procesamiento, los problemas con el aumento de escala, la seguridad, etc.?

De acuerdo con la base de datos del Chemical Abstracts Registry®, las únicas sales de bupropion de las que se ha informado previamente son las sales de clorhidrato (HCl), (2Z)-2-butenodioato, (2E)-2-butenodioato, metanosulfonato, ácido fórmico, 2-hidroxi-1,2,3-propanotricarboxilato, fosfato y de trifluorometanosulfonato.

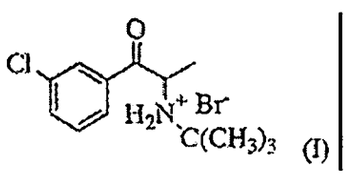
Existe la necesidad de una formulación de una sal farmacéuticamente aceptable de bupropion para administrar una vez al día con estabilidad mejorada.

RESUMEN

La presente invención se relaciona con las formas farmacéuticas que comprenden una cantidad eficaz de una sal farmacéuticamente aceptable de bupropion (bromhidrato de bupropion) que es más estable que el clorhidrato de bupropion. En particular dichas composiciones de bupropion son más estables que otras composiciones de clorhidrato de bupropion, por lo demás equivalentes, cuando se almacenan durante al menos 3 meses y/o al menos 6 meses a 40 grados C y 75 % de humedad relativa ("condiciones de almacenamiento acelerado") como se demuestra por una cantidad reducida de al menos una porción característica de la degradación de bupropion y/o por presentar menos fluctuación o reducción en la concentración después de haber estado almacenadas durante al menos 3 meses y/o al menos 6 meses en condiciones de almacenamiento acelerado en relación con una composición de clorhidrato de bupropion, por lo demás similar, como se demuestra por ejemplo por una menor fluctuación en el perfil de disolución in vitro en al menos un medio de disolución durante un período de 24 horas.

La presente invención también se relaciona con el uso de dichas formas farmacéuticas de bromhidrato de bupropion más estables para el tratamiento de una o más afecciones en un sujeto.

Las formas farmacéuticas de la presente invención comprenden un compuesto de fórmula I (bromhidrato de bupropion):



(I)

y vehículos, excipientes y/o diluyentes farmacéuticamente aceptables, donde dicha composición tiene mayor estabilidad que una composición farmacéutica correspondiente que comprende clorhidrato de bupropion y

vehículos, excipientes y/o diluyentes farmacéuticamente aceptables.

En otras realizaciones de la presente invención, la sal de bupropion puede estar en forma de sus formas anhidras, hidratadas y solvatadas, en forma de profármacos y en los enantiómeros individualmente ópticamente activos de la sal de bupropion, como por ejemplo (+)-bupropion y (-)-bupropion. Las sales de bupropion farmacéuticamente aceptables adecuadas para usar en la presente invención son más estables que el clorhidrato de bupropion. Las sales de bupropion adecuadas también incluyen por ejemplo, las sales de adición de ácido farmacéuticamente aceptables. En ciertas realizaciones, la sal de adición de ácido de bupropion se puede obtener indirectamente mediante la adición por separado de bupropion y un ácido a la formulación del núcleo.

Otra realización de la presente invención contempla el uso de bromhidrato de bupropion para preparar un medicamento destinado a tratar una afección que puede beneficiarse de la administración de bupropion, según la cual dicho medicamento tiene mayor estabilidad que un medicamento correspondiente que comprende el clorhidrato de bupropion. En este documento, estabilidad mejorada significa que la sal o una composición que la contiene es más estable después de haber sido almacenada durante al menos 3 meses y/o 6 meses a 40 grados C y 75 % de humedad relativa (condiciones de almacenamiento acelerado) como se demuestra por una menor cantidad de al menos una porción característica de la degradación de bupropion y/o una reducción o fluctuación en la concentración demostrada por ejemplo, por una mayor fluctuación en el perfil de disolución in vitro en un período de al menos 12 ó 24 horas en al menos un medio de disolución en relación con, y en las mismas condiciones que, una composición de bromhidrato de bupropion, por lo demás equivalente, almacenada durante el mismo período de tiempo en las mismas condiciones de almacenamiento acelerado.

Según se trata más adelante y se conoce en general en el área el medio de disolución y las condiciones adecuadas para analizar las características de disolución de las

formas farmacéuticas como los comprimidos son bien conocidos por los técnicos en la materia y están contenidos 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 (Método de la Cesta Rotatoria) en 900 ml de agua; HCl 0,1 N; HCl 0,1 N + Cetrimida 0,1 %; solución 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 solución amortiguadora de fosfato de pH 7,4 a 75 RPM a 37 grados C +/- 0,5 grados C.

Además, otros medios de disolución incluyen los medios de disolución USP-3 y las condiciones de disolución USP-3 es decir, LGS de pH 1,2; solución amortiguadora de acetato de pH 4,5 y solución amortiguadora de fosfato de pH 6,8.

En otra realización de la presente invención, las formas farmacéuticas que comprenden bromhidrato de bupropion se pueden usar para tratar una afección que se puede beneficiar de la administración de bupropion como la depresión, el trastorno afectivo estacional, el abandono del hábito de fumar o la obesidad.

Otra realización de la presente invención contempla el uso de bromhidrato de bupropion para preparar un comprimido de liberación modificada de bromhidrato de bupropion con estabilidad mejorada. Los comprimidos de la presente invención, que comprenden bromhidrato de bupropion, tienen una inesperada estabilidad mejorada en comparación con los comprimidos del estado anterior de la técnica de clorhidrato de bupropion.

En otra realización la presente invención contempla el uso de bromhidrato de bupropion para producir comprimidos que se pueden administrar una vez al día u otras formas farmacéuticas que son bioequivalentes, según definen los criterios de la FDA, a los comprimidos de Wellbutrin™ o Zyban/Wellbutrin™ SR cuando se administran una vez al día a un sujeto que lo necesita. En particular, al menos uno de Tmáx, Cmáx y perfil de AUC están dentro del 80 % al 125 % de los de Wellbutrin™ y Zyban™/Wellbutrin™ cuando se administran una vez al día a un sujeto que lo necesita. Preferentemente, estas formulaciones también

carecerán de cualquier efecto importante por el consumo de alimentos.

Además la presente invención proporciona formas farmacéuticas de bromhidrato de bupropion que contienen al menos un recubrimiento, por ejemplo, comprimidos, que son resistentes a la absorción rápida en concentración elevada de alcohol, por ejemplo, 40 % de etanol, debido a la presencia de un recubrimiento apropiado, es decir, un SmartCoat™.

Otra realización de la presente invención contempla además un método para preparar un medicamento para el tratamiento de una afección que se puede beneficiar de la administración de bupropion que comprende poner en contacto una cantidad eficaz de bromhidrato de bupropion con uno o más vehículos, diluyentes y/o excipientes farmacéuticamente aceptables.

Otra realización de la presente invención contempla un método para tratar una afección que se puede beneficiar de la administración de bupropion, que comprende la administración a un sujeto de una cantidad eficaz de bromhidrato de bupropion. Por ejemplo, dichas afecciones que se pueden beneficiar de la administración de bromhidrato de bupropion incluyen pero no exclusivamente, la depresión, inclusive el trastorno afectivo estacional, los síntomas cognoscitivos de la depresión, la depresión bipolar, la depresión posparto, la depresión menor, la falta de energía en la depresión, la depresión suicida, los trastornos de ansiedad, el trastorno de ansiedad generalizado, el trastorno de ansiedad social, el trastorno obsesivo compulsivo, el trastorno de estrés post traumático (TEPT), el trastorno de pánico, los trastornos que requieren un efecto estimulante, el trastorno de hiperactividad por déficit atencional (THDA), la narcolepsia, la hipersomnia, los trastornos de abuso de fármacos, la dependencia de estimulantes, la dependencia de marihuana, la dependencia de nicotina, la obesidad, la disfunción sexual femenina y masculina como la eyaculación precoz, el síndrome premenstrual, el trastorno disfórico premenstrual, el dolor neuropático, la fibromialgia, la neuropatía diabética, la infección viral, la apnea del sueño, los trastornos del sueño y las

migrañas. Las afecciones pueden estar focalizadas en diferentes poblaciones demográficas, como los trastornos reproductivos relacionados con el estado de ánimo, los trastornos específicos de la edad de las poblaciones y los trastornos específicos de la raza de las poblaciones.

De acuerdo con un aspecto de la invención, se proporciona una composición para la administración a un sujeto que necesita de tratamiento para una afección. La composición comprende una cantidad farmacéuticamente eficaz de una sal de bupropion que es más estable que el clorhidrato de bupropion según se define aquí. Además, la composición es más estable que una composición correspondiente que comprenda clorhidrato de bupropion.

La presente invención incluye medicamentos tanto orales como no orales que contienen bromhidrato de bupropion. Antes de la presente invención no se disponía de medicamentos que contuvieran bromhidrato de bupropion. Particularmente, la invención abarca composiciones adecuadas para administración tópica, inyectable, por inhalación y otras vías de administración. De manera característica los medicamentos de la presente invención se pueden administrar por vía oral.

En particular la invención incluye formulaciones de liberación extendida. En otro aspecto, la presente invención incluye formulaciones de liberación retardada. Además, la presente invención abarca formulaciones de absorción mejorada.

En una realización particular, las composiciones de la invención incluyen formulaciones de comprimidos de matriz de liberación controlada.

En una implementación más particular de la invención, la composición de un medicamento de bupropion de acuerdo con la invención puede comprender (i) un núcleo que incluye bromhidrato de bupropion, un aglutinante y un lubricante; y (ii) un recubrimiento de control de la liberación que prácticamente rodea dicho núcleo; donde dicha composición proporciona una liberación controlada de dicho bromhidrato de bupropion. Dicha composición puede contener opcionalmente uno o más recubrimientos

adicionales rodeando el núcleo y/o el recubrimiento de control de la liberación como los recubrimientos de barrera contra la humedad, los recubrimientos entéricos o los recubrimientos que afectan a la integridad y/o el aspecto físicos del bupropion. El aglutinante se puede seleccionar entre los aglutinantes farmacéuticos conocidos como el alcohol polivinílico. El lubricante también se puede seleccionar entre los lubricantes farmacéuticos conocidos como el behenato de glicerilo. El recubrimiento de control de la liberación puede incluir un polímero insoluble en agua, un polímero soluble en agua y opcionalmente un plastificante. El polímero insoluble en agua se puede seleccionar entre una variedad de polímeros insolubles en agua útiles en composiciones farmacéuticas de liberación extendida como la etilcelulosa. El polímero soluble en agua se puede seleccionar entre una variedad de polímeros solubles en agua útiles en composiciones farmacéuticas de liberación extendida como polivinilpirrolidona. El plastificante cuando está presente se puede seleccionar entre una variedad de plastificantes conocidos como las mezclas de polietilenglicol 4000 y sebacato de dibutilo. Estas composiciones incluyen composiciones que se pueden administrar una vez al día que son bioequivalentes a Wellbutrin™ o los comprimidos de Zyban™/Wellbutrin™ SR cuando se los administra una vez al día a un sujeto que los necesita pueden ser bioequivalentes. Opcionalmente, estas composiciones pueden no presentar un efecto por el consumo de alimentos y/o pueden ser resistentes a la absorción rápida del fármaco en presencia de concentraciones de alcohol elevadas (es decir, 40 % en peso de etanol).

En una implementación más particular de la invención, la composición de bupropion del tema comprende (i) un núcleo que contiene bromhidrato de bupropion, un aglutinante y un lubricante; y (ii) un recubrimiento de control de la liberación que prácticamente rodea dicho núcleo; donde dicho recubrimiento de control de la liberación incluye una dispersión acuosa de un copolímero de un éster neutro sin ningún grupo funcional, un poliglicol con un punto de fusión mayor de 55 °C y uno o más excipientes farmacéuticamente aceptables, donde dicho recubrimiento se deposita recubriendo dicho núcleo y se cura a una

temperatura al menos igual o mayor que el punto de fusión del poliglicol. Opcionalmente, este medicamento puede comprender uno o más recubrimientos adicionales rodeando el núcleo y/o un recubrimiento de control de la liberación como recubrimientos de barrera contra la humedad, recubrimientos entéricos, recubrimientos que excluyen la absorción rápida de la dosis en medios específicos como el alcohol, y recubrimientos que afectan a la estabilidad o la integridad físicas del medicamento y/o su aspecto físico.

En una implementación en particular de la invención, la composición de bupropion del tema comprende multiparticulados.

En una implementación particular de la invención, la composición de bupropion del tema comprende un segundo fármaco. El segundo fármaco puede ser cualquier fármaco que se pueda administrar en combinación con la sal de bupropion del tema como otros antidepresivos, ISRS, ansiolíticos, etc. La invención abarca combinaciones de fármacos donde el segundo fármaco puede producir un beneficio sinérgico en la eficacia de bupropion así como combinaciones de fármacos no sinérgicos. En particular la invención abarca composiciones de bromhidrato de bupropion en las que el segundo fármaco es citalopram, escitalopram y/o venlafaxina.

Según otro aspecto de la invención, se proporciona un método de uso de una composición de acuerdo con cualquiera de las reivindicaciones precedentes para el tratamiento de un sujeto que necesita dicha administración. Esto incluye en particular el tratamiento de la depresión, la obesidad y los trastornos de abuso como la adicción a la nicotina y el abandono del hábito de fumar. En una realización de ejemplo tales tratamientos comprenden regímenes de administración de una vez al día.

Según otro aspecto de la invención, se proporciona un uso del bromhidrato de bupropion para preparar un medicamento para tratar las afecciones que se benefician de la administración de bupropion, donde dicho medicamento

tiene mayor estabilidad que un medicamento correspondiente que comprende clorhidrato de bupropion.

De conformidad con un aspecto de la presente invención, se proporciona un comprimido de liberación controlada, que comprende (i) un núcleo que contiene una cantidad eficaz de bromhidrato de bupropion, un aglutinante, un lubricante; y (ii) un recubrimiento de control de la liberación rodeando dicho núcleo; y opcionalmente (iii) una barrera contra la humedad rodeando dicho recubrimiento de control de la liberación o el núcleo; y; según el cual el comprimido de liberación extendida presenta un perfil de disolución tal que después de 2 horas, se libera no más de 20 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera de 2 % a 18 %, de 4 % a 8 % o 5% del contenido de bromhidrato de bupropion después de 2 horas; después de 4 horas, se libera de 15 % a 45 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera de 21 % a 37 %, de 28 % a 34 % o 32 % del contenido de bromhidrato de bupropion después de 4 horas; después de 8 horas, se libera de 40 % a 90 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera de 60 % a 85 %, de 68 % a 74 %, o 74 % del contenido de bromhidrato de bupropion después de 8 horas; y después de 16 horas se libera no menos de 80 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera no menos de 93 %, no menos de 96 %, o no menos de 99 % del contenido de bromhidrato de bupropion después de 16 horas; y donde la sal bromhidrato de bupropion contenida en dicho comprimido de liberación extendida tiene mayor estabilidad que un comprimido que tiene la misma composición salvo que el bromhidrato de bupropion es reemplazado por clorhidrato de bupropion.

En otro aspecto la composición presenta un perfil de disolución tal que después de 2 horas se libera no más de 40 % del bromhidrato de bupropion, por ejemplo, 33 %, después de 4 horas se libera de 40 % a 75 %, por ejemplo, 59 % del bromhidrato de bupropion, después de 8 horas se libera no menos de 75 % del bromhidrato de bupropion, por ejemplo, 91 % y después de 16 horas se libera no menos de 85 % del bromhidrato de bupropion, por ejemplo, 97 %.

Estos medicamentos comprenderán típicamente de 50 a 500 mg de bromhidrato de bupropion. En las realizaciones de ejemplo divulgadas aquí el medicamento contiene 174 mg o 348 mg de bromhidrato de bupropion.

De conformidad con otro aspecto de la presente invención, se proporciona un comprimido de absorción mejorada, que comprende (i) un núcleo que contiene una cantidad eficaz de bromhidrato de bupropion, un aglutinante, un lubricante; y (ii) un recubrimiento de control de la liberación rodeando dicho núcleo; y donde el comprimido de absorción mejorada presenta un perfil de disolución tal que después de 2 horas, se libera no más de 25 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera de 10 % a 20 % del contenido de bromhidrato de bupropion después de 2 horas; después de 4 horas, se libera de 25 % a 55 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera de 30 % a 50 %, del contenido de bromhidrato de bupropion después de 4 horas; después de 8 horas, se libera más de 60 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera de 70 % a 90 % del contenido de bromhidrato de bupropion después de 8 horas; y después de 16 horas se libera más de 70 % del contenido de bromhidrato de bupropion, por ejemplo en ciertas realizaciones se libera más de 80 % del contenido de clorhidrato de bupropion después de 16 horas; y donde dicho comprimido de liberación extendida tiene mayor estabilidad que un comprimido que tiene la misma composición salvo que el bromhidrato de bupropion es reemplazado por clorhidrato de bupropion. Esta composición puede comprender además opcionalmente uno o más recubrimientos rodeando el núcleo y/o el recubrimiento de control de la liberación.

En una realización de ejemplo esta composición puede comprender un perfil de disolución tal que después de 2 horas libera no más de 40 % de bromhidrato de bupropion, por ejemplo, 33 %; después de 4 horas libera de 40 % a 75 % de bromhidrato de bupropion, por ejemplo, 59 %, después de 8 horas libera no menos de 75 % de bromhidrato de bupropion, por ejemplo, 91 % y después de 16 horas

libera no menos de 85 % de bromhidrato de bupropion, por ejemplo, 97 %.

De conformidad con otro aspecto de la invención se proporciona una sal de bupropion y sus formas polimórficas que tienen una estabilidad mejorada donde la sal es bromhidrato, y donde estabilidad mejorada se refiere a la formación reducida de al menos un producto de degradación característico de la degradación de bupropion y/o a la mayor retención de la concentración como se demuestra por ejemplo, por una fluctuación reducida en el perfil de disolución in vitro en al menos un medio de disolución con relación a una formulación que contiene clorhidrato de bupropion, por lo demás equivalente, cuando las formulaciones que contienen estas sales de bupropion se almacenan durante períodos prolongados en condiciones equivalentes. En particular estabilidad mejorada se refiere a composiciones de bromhidrato de bupropion que están menos sujetas a la degradación que una composición de clorhidrato de bupropion, por lo demás equivalente, cuando se almacenan en condiciones de almacenamiento acelerado, es decir, 40 grados C a 75 % de humedad relativa durante al menos 3 meses, y/o durante al menos 6 meses o más y/o que presentan menos fluctuación o reducción en la concentración como lo prueba una fluctuación reducida en el perfil de disolución in vitro en al menos un medio de disolución en el que la disolución se efectúa en las mismas condiciones después que las composiciones de bromhidrato de bupropion y de clorhidrato de bupropion se almacenan durante al menos 3 meses y/o al menos 6 meses a 40 grados C y 75 % de humedad relativa. En la presente invención, según se describe más adelante, la degradación se analiza basándose en la cantidad de al menos un compuesto característico de la degración de bupriopion.

Más particularmente, la presente invención abarca un comprimido de absorción mejorada, que comprende (i) un núcleo que contiene una cantidad eficaz de bupropion HBr, un aglutinante, un lubricante; y (ii) un recubrimiento de control de la liberación rodeando dicho núcleo; donde el comprimido de absorción mejorada presenta un perfil de disolución tal que después de 2 horas, se libera no más de 40 % de bupropion, (p. ej., 33 %); después de 4 horas,

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se libera de 40 % a 75 % de bupropion, (p. ej., 59 %), después de 8 horas, se libera al menos 75 % (p. ej., 91 %); y después de 16 horas al menos 85 % (p. ej., 97 %).

Según se trata más adelante, la disolución in vitro de bupropion de las formulaciones de liberación controlada o extendida de acuerdo con la invención se puede determinar mediante métodos bien conocido por los técnicos con experiencia en el área farmacéutica. La farmacopea de los Estados Unidos (USP) así como sus contrapartes europea y japonesa contienen métodos adecuados que se ejemplifican más adelante. Esto incluye a modo de ejemplo efectuar la disolución en un aparato 1 de la USP (Método de la cesta de tipo rotatorio) en 900 ml de agua, HCl 0,1 N, HCl 0,1 N + Cetrimida al 0,1 %, solución amortiguadora de la USP de pH 1,5, solución amortiguadora de acetato de pH 6,5, solución amortiguadora de fosfato de pH 7,4 a 75 RPM a 37 grados C +/- 0,5 grados C o efectuar la disolución usando un medio de disolución USP-3 como 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.

BREVE DESCRIPCIÓN DE LAS FIGURAS

La Figura 1 muestra un perfil de DVS (sorción dinámica de vapor, por sus siglas en inglés) para el bromhidrato de bupropion (HBr).

La Figura 2 muestra los datos de la isoterma de DVS para bupropion HBr.

La Figura 3 es un gráfico de barras que muestra los resultados de la prueba de estabilidad de las sales de bupropion mezcladas con excipientes en viales cerrados durante 20 días a 40°C/75 % de humedad relativa (HR).

La Figura 4 es un gráfico de barras que muestra la concentración de las sales de bupropion mezcladas con excipientes después del almacenamiento en viales cerrados durante 20 días a 40°C/75 % de HR en comparación con sus concentraciones iniciales.

La Figura 5 es un gráfico de barras que muestra la concentración de las sales de bupropion mezcladas con excipientes y agua después del almacenamiento en viales cerrados durante 32 días a 40°C en comparación con sus concentraciones iniciales.

La Figura 6 es un gráfico de barras que muestra la concentración de las sales de bupropion mezcladas con excipientes, agua, alcohol isopropílico y etanol después del almacenamiento en viales cerrados durante 32 días a 40°C en comparación con sus concentraciones iniciales.

La Figura 7 es un gráfico de barras que muestra la concentración de las sales de bupropion mezcladas con excipientes, alcohol isopropílico y etanol después del almacenamiento en viales cerrados durante 32 días a 40°C en comparación con sus concentraciones iniciales.

La Figura 8 es un gráfico de barras que muestra el % de impurezas para las sales de bupropion mezcladas con excipientes y tratadas durante 32 días en viales cerrados y con agregado de cantidades conocidas de agua.

La Figura 9 es un gráfico de barras que muestra el % de impurezas para las sales de bupropion mezcladas con excipientes y tratadas durante 32 días en viales cerrados y con agregado de cantidades conocidas de agua, alcohol isopropílico (AIP) y etanol (EtOH).

La Figura 10 es un gráfico de barras que muestra el % de impurezas para las sales de bupropion mezcladas con excipientes y tratadas durante 32 días en viales cerrados y con agregado de cantidades conocidas de alcohol isopropílico (AIP) y etanol (EtOH).

La Figura 11 es un diagrama de flujo que muestra el proceso global de desarrollo de los comprimidos XL de bupropion HBr.

La Figura 12 es un diagrama de flujo que demuestra el proceso de granulación de los comprimidos XL y EA de bupropion HBr.

La Figura 13 es un diagrama de flujo que muestra el proceso global de obtención de los comprimidos XL de bupropion HBr.

La Figura 14 es un diagrama de flujo que muestra el proceso global de recubrimiento de bupropion HBr XL.

La Figura 15 es un perfil de disolución de los comprimidos de 4 kp, de 6 a 7 kp y de 9 a 10 kp, que compara los efectos de la dureza sobre la disolución en el estudio sobre el lote BUP-HBr-XL-009-5.

La Figura 16 es un perfil de disolución de los núcleos de bupropion HBr de 348 mg que se comprimieron usando punzones de 9 mm en el estudio sobre el lote BUP-HBr-XL-009-5.

La Figura 17 es un perfil de disolución de los núcleos de bupropion HBr de 348 mg que se comprimieron usando punzones de 10 mm en el estudio sobre el lote BUP-HBr-XL-009-5.

La Figura 18 es una comparación de perfiles de disolución de los núcleos de 9 mm y 10 mm de diámetro de 348 mg de bupropion HBr en el estudio sobre el lote BUP-HBr-XL-009-5.

La Figura 19 es un perfil de disolución de los de 174 mg en el estudio sobre el lote BUP-HBr-XL-021-5.

La Figura 20 es un perfil de disolución de BUP-HBr-XL-348 mg-013-5 (con 28 mg, 30 mg, 32 mg y 34 mg de aumento de peso).

La Figura 21 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).

La Figura 22 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 23 es un perfil de disolución de BUP-HBr-XL-348 mg-018-5 (con 7 mg de aumento de peso).

La Figura 24 es un perfil de disolución de BUP-HBr-XL-174 mg-022-5 (con 22 mg, 24 mg, 28 mg y 30 mg de aumento de peso).

La Figura 25 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 26 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).

La Figura 27 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 28 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 29 es un perfil de disolución de BUP-HBr-XL-348 mg-026-5 (con 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso).

La Figura 30 es un perfil de disolución de BUP-HBr-XL-174 mg-027-5 (con 22 mg, 24 mg y 26 mg de aumento de peso).

La Figura 31 es un perfil de disolución de BUP-HBr-XL-174 mg-027-5 (con 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso).

La Figura 32 es un diagrama de flujo que muestra el proceso global de desarrollo de los comprimidos EA de bupropion HBr.

La Figura 33 es un diagrama de flujo que demuestra el proceso de granulación de los comprimidos EA de bupropion HBr.

Figura 34 es un diagrama de flujo que muestra el proceso de compresión de los comprimidos EA de 300 mg y 150 mg de bupropion HBr.

La Figura 35 es un diagrama de flujo que muestra el proceso de recubrimiento de los comprimidos EA de 150 mg y 300 mg de bupropion HBr con un recubrimiento de Ethocel™.

La Figura 36 es un perfil de disolución de los núcleos de los comprimidos a diferentes niveles de dureza (4 kp, 6 a 7 kp y 9 kp) en el estudio sobre el lote BUP-HBr-XL-016-5.

La Figura 37 es un perfil de disolución de los núcleos EA de bupropion HBr de 300 mg en el estudio sobre el lote BUP-HBr-XL-016-5.

La Figura 38 es un perfil de disolución de los núcleos de bupropion HBr de 150 mg en el estudio sobre el lote BUP-HBr-XL-016-5.

La Figura 39 es un perfil de disolución de BUP-HBr-EA-300 mg-001-5 (con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso).

La Figura 40 es un perfil de disolución USP3 comparativo de los comprimidos EA de bupropion HBr de 300 mg con 52 mg de aumento de peso con los perfiles in vivo e in vitro del comprimido de referencia (bupropion HCl de 300 mg).

La Figura 41 es un perfil de disolución de BUP-HBr-EA-150 mg-002-5 (con 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg y 36 mg de aumento de peso).

La Figura 42 es un perfil de disolución de BUP-HBr-EA-300 mg-003-5 (con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso).

La Figura 43 es un perfil de disolución de BUP-HBr-EA-300 mg-004-5 (con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso).

La Figura 44 es un perfil de disolución de BUP-HBr-EA-300 mg-005-5 (con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso).

La Figura 45 es un perfil de disolución de BUP-HBr-EA-150 mg-006-5 (con 24 mg, 28 mg, 32 mg, 34 mg y 36 mg de aumento de peso).

La Figura 46 es un perfil de disolución USP3 comparativo de los comprimidos EA de 150 mg de bupropion HBr con 24 y

34 mg de aumento de peso con los perfiles in vivo e in vitro del comprimido de referencia (bupropion HCl de 300 mg).

La Figura 47 es un gráfico de barras que muestra el % de impurezas para los comprimidos XL de bupropion HCl de 300 mg y de los comprimidos EC recubiertos de bupropion HBr de 348 mg a 40°C y 75 % de humedad relativa.

La Figura 48 es un gráfico de barras que muestra el % de impurezas para los comprimidos de bupropion HCl de 300 mg (Wellbutrin XL) y los comprimidos XL finales de bupropion HBr de 348 mg a 40°C y 75 % de humedad relativa.

La Figura 49 contiene gráficos de barras que muestran los % de 3-CBA formada en estudios de degradación forzada de clorhidrato de bupropion (HCl) frente a bupropion HBr en presencia de excipientes.

La Figura 50 contiene gráficos de barras que muestran el % de 852U77 formada en estudios de degradación forzada de bupropion HCl frente a bupropion HBr en presencia de excipientes.

La Figura 51 contiene gráficos de barras que muestran el % de 20U78 formada en estudios de degradación forzada de bupropion HCl frente a bupropion HBr en presencia de excipientes.

La Figura 52 contiene gráficos de barras que muestran el % de 827U76 formada en estudios de degradación forzada de bupropion HCl frente a bupropion HBr en presencia de excipientes.

La Figura 53 es un gráfico que muestra la pérdida de IFA en un experimento de análisis termogravimétrico (TGA, por sus siglas en inglés) a 100 °C de bupropion HCl frente a bupropion HBr.

La Figura 54 es un gráfico que muestra la difracción relativa de rayos X de polvo (PXRD, por sus siglas en inglés) para la forma polimórfica I de bromhidrato de bupropion.

La Figura 55 es un gráfico que muestra el perfil de calorimetría diferencial de barrido (DSC, por sus siglas en inglés) de la forma polimórfica I de bromhidrato de bupropion.

La Figura 56 es un gráfico que muestra el PXRD relativo para la forma polimórfica II de bromhidrato de bupropion.

La Figura 57 es un gráfico que muestra el perfil de DSC de la forma polimórfica II de bromhidrato de bupropion.

La Figura 58 es un gráfico que muestra el PXRD relativo para la forma polimórfica III de bromhidrato de bupropion.

La Figura 59 es un gráfico que muestra el perfil de DSC de la forma polimórfica III de bromhidrato de bupropion.

La Figura 60 es un gráfico de la PXRD relativa de una muestra de la forma polimórfica I de bromhidrato de bupropion después de 6 meses en las condiciones de la ICH (Conferencia Internacional sobre Armonización de Requisitos Técnicos para el Registro de Productos Farmacéuticos Para uso Humano) (40°C, 75 % de HR).

La Figura 61 es un gráfico de la PXRD de una muestra de la forma polimórfica II de bromhidrato de bupropion después que 1 mes en las condiciones de la ICH (40°C, 75 % de HR).

La Figura 62 es un gráfico de la PXRD de una muestra de la forma polimórfica III de bromhidrato de bupropion después que 1 mes en las condiciones de la ICH (40°C, 75 % de HR).

La Figura 63 contiene los resultados de los estudios de estabilidad del núcleo de bupropion HBr XL 174 mg (Lote del núcleo N° Bup-HBr-XL-004-5); el núcleo de bupropion HBr XL 348 mg (Lote del núcleo N° Bup-HBr-XL-009-5); el núcleo de bupropion HCl XL de 150 mg (Lote N° 05E056) y el núcleo de bupropion HCl XL de 300 mg (Lote N° 05D380) inicialmente, después de 10 días abiertos y cerrados y después de 20 días abiertos y cerrados. Allí se muestra el % de impurezas 3-CBZ, 852U77, 20U78dilu, 827U76.

La Figura 64 y la Figura 65 contienen respectivamente los datos de estabilidad para los comprimidos XL de bupropion HBr de 348 mg (Lote N° Bup-HBr-XL-348-025-5) y los comprimidos EA de bupropion HBr de 300 mg (Lote N° Bup-HBr-EA-300-001-5) inicialmente y después de 3 meses, 6 meses, 9 meses y 12 meses en condiciones de almacenamiento acelerado (40 grados C y 75 % de humedad relativa). El ensayo determinó la cantidad de impurezas 3-CBA, 852U77, 20U78/diluyente, 827U76 y también comparó los perfiles de disolución y el aspecto de ellas.

La Figura 66 compara los perfiles de disolución y de liberación del fármaco in vitro de los comprimidos (finales) de Bupropion HBr XL de 348 mg Lote N° Bup-HBr-XL-012-5, los comprimidos finales de 300 mg de Wellbutrin XL (Lote N° 05A116), los comprimidos (ECI) de Bupropion HBr XL de 348 mg Lote N° Bup-HBr-XL-012-5 (EC 32 mg de

peso) y los comprimidos (ECI) de Wellbutrin XL de 300 mg (Lote N° 05D047) en diferentes medios USP-3 (LGS de pH 1,2, solución amortiguadora de acetato de pH 4,5 y solución amortiguadora de fosfato de pH 6,8) durante un período de 16 horas.

La Figura 67 compara los perfiles de disolución y de liberación del fármaco de Bupropion HBr de 348 mg Lote N° 05E304 en diferentes medios USP-3 (LGS de pH 1,2, solución amortiguadora de acetato de pH 4,5, solución amortiguadora de fosfato o LIS (líquido intestinal simulado) de pH 6,8) en un período de 16 horas y además compara este perfil de liberación frente al perfil de liberación para Bup 300 XL de referencia (01L238) in vivo y BUP 300 XL de referencia (01L238) in vitro en medio USP-3.

La Figura 68 contiene perfiles de disolución comparativos para Bupropion HBr XL de 348 mg y Wellbutrin XL (final y EC) en medio USP-3 (LGS de pH 1,2, solución amortiguadora de acetato de pH 4,5 y solución amortiguadora de fosfato de pH 6,8) en un período de 16 horas.

DEFINICIONES

La expresión "sal de bupropion" tiene aquí su significado corriente e incluye todas las sales de bupropion.

La expresión "sal de buropion que es más estable que el clorhidrato de bupropion" hace referencia a una sal de bupropion o una composición que la contiene que está menos sujeta a degradación que una sal de clorhidrato de bupropion, por lo demás equivalente, o una composición que la contiene cuando se las almacena durante al menos 3 meses, 4 meses, 5 meses y/o al menos 6 meses en condiciones de almacenamiento acelerado (40 grados C y 75 % de humedad relativa), y/o cuando se las almacena durante al menos 3, 4, 5 y/o 6 meses en condiciones de almacenamiento acelerado (40 grados C y 75 % de humedad relativa) y/o que presentan menos de una reducción o fluctuación en la concentración según se demuestra por menos fluctuación en el perfil de disolución in vitro en al menos un medio de disolución con relación a una composición de clorhidrato de bupropion, por lo demás similar, donde la disolución se efectúa en las mismas condiciones después que estas composiciones se almacenan durante al menos 3, 4, 5 ó 6 meses a 40 grados C y 75 %

de humedad relativa. Particularmente, las sales de bromhidrato de bupropion y sus polimorfos pueden originar formulaciones de bupropion que presenten perfiles de disolución en el tiempo que están menos sujetos a la fluctuación cuando se almacenan en condiciones de almacenamiento acelerado por períodos prolongados, es decir, al menos 3, 4, 5 ó 6 meses a 40 grados C y 75 % de humedad relativa.

Las expresiones "activo", "principio activo", "principio farmacéutico activo", "fármaco activo" o "fármaco" como se usan aquí significan cualquier ingrediente farmacéutico activo ("IFA"), incluidas sus sales farmacéuticamente aceptables (p. ej. las sales de clorhidrato, las sales de bromhidrato, las sales de yodhidrato y las sales de sacarinato), así como en las formas anhidras, hidratadas y solvatadas, en forma de profármacos y de los enantiómeros individualmente ópticamente activos aceptables desde el punto de vista farmacéutico del IFA así como los polimorfos del IFA.

La expresión "absorción rápida" hace referencia a la liberación rápida de un fármaco de un medicamento en determinadas condiciones como condiciones disolventes p. ej., concentración de etanol elevada (40 %).

Las expresiones "otro fármaco" o "segundo fármaco" como se usan aquí significan un fármaco diferente de bupropion, incluidos pero no exclusivamente, antidepresivos, otros fármacos neurosiquiátricos, vasodilatores, ansiolíticos, moduladores del apetito, moduladores del sueño, ISRS, antivirales, analgésicos, antijaquecosos, antiinflamatorios (tanto esteroideos como no esteroideos) y más particularmente pueden incluir citalopram, escitalopram, venlafaxina, clozapina, melperona, amperozida, iloperidona, risperidona, quetiapina, olanzapina, ziprasidona, aripiprazol, reboxetina, Viagra®, sertralina, paroxetina, fluoxetina, gabapentina, ácido valproico, amitriptilina, lofepramina, fluvoxamina, imipramina, mirtazapina, nefazodona, nortriptilina, SAM-E y combinaciones de éstos y sus sales farmacéuticamente aceptables (p. ej., las sales de clorhidrato, las de sales bromhidrato, las sales de yodhidrato y las sales de sacarinato), así como en las

formas anhidras, hidratadas y solvatadas, en forma de profármacos y de los enantiómeros individualmente ópticamente activos del fármaco.

Los términos "formulación" o "composición" como se usan aquí se refieren al fármaco en combinación con vehículos y otros ingredientes inertes farmacéuticamente aceptables. Esto incluye formulaciones que se pueden administrar por vía oral así como formulaciones administrables por otras vías.

La expresión "forma farmacéutica" como se usa aquí se define con el significado de una preparación farmacéutica en las que se incluyen dosis del fármaco activo.

"Formas farmacéuticas de liberación modificada" se usa aquí según la definición de la Farmacopea de los Estados Unidos (USP) como aquellas cuyas características de liberación del fármaco en el transcurso del tiempo y/o la ubicación se eligen de modo de conseguir objetivos terapéuticos o de conveniencia que no son ofrecidos por las formas farmacéuticas de liberación inmediata o de matriz de liberación normal sin recubrir, convencionales. La velocidad de liberación del fármaco activo de una forma farmacéutica de liberación modificada es controlada por características de la forma farmacéutica y/o en combinación con condiciones fisiológicas o ambientales en vez de solamente por las condiciones fisiológicas o ambientales. Las formas farmacéuticas de liberación modificada de la invención pueden ser contrastadas con las formas farmacéuticas de liberación inmediata o de matriz de liberación normal, sin recubrir, convencionales, que producen de manera característica grandes relaciones de concentración máxima/mínima plasmática de fármaco (Cmáx/Cmín) debidas a la absorción rápida del fármaco en el organismo (es decir, in vivo, en relación con el índice terapéutico del fármaco; es decir, la relación de la concentración máxima de fármaco necesaria para producir y mantener una respuesta farmacológica deseable). En las formas farmacéuticas de liberación inmediata o de matriz de liberación normal, no recubiertas, convencionales, el contenido de fármaco se libera en el tubo digestivo en un período corto, y los niveles plasmáticos de fármaco alcanzan el máximo poco

después de la dosificación. El diseño de las formas farmacéuticas de liberación inmediata o de matriz de liberación normal, sin recubrir, convencionales, se basa en general en conseguir la mayor velocidad de liberación posible del fármaco, y por consiguiente su absorción, a menudo a riesgo de crear efectos colaterales indeseables relacionados con la dosis. Por otra parte, las formas farmacéuticas de liberación modificada de la invención, mejoran el valor terapéutico del fármaco activo al reducir la relación entre la concentración máxima/mínima de fármaco en el plasma (Cmáx/Cmín) mientras mantienen los niveles plasmáticos del fármaco dentro de la ventana terapéutica. Las formas farmacéuticas de liberación modificada de la invención intentan administrar una cantidad terapéuticamente eficaz de sal de bupropion y combinaciones de ésta como una dosis una vez al día para que la relación Cmáx/Cmín en el plasma en el estado estacionario sea menor que el índice terapéutico y para mantener los niveles de fármaco a niveles eficaces constantes para proporcionar un beneficio terapéutico durante un período de veinticuatro horas. Por consiguiente, las formas farmacéuticas de liberación modificada de la invención evitan grandes fluctuaciones entre las concentraciones máxima y mínima que se ven normalmente con las formas farmacéuticas de liberación inmediata o convencionales y pueden proporcionar una curva de concentración sérica sustancialmente plana a lo largo de todo el período terapéutico. Las formas farmacéuticas de liberación modificada se pueden diseñar para proporcionar un aumento rápido de la concentración plasmática de la sal de bupropion que permanece sustancialmente constante dentro del intervalo terapéutico de la sal de bupropion durante un período de al menos veinticuatro horas. Alternativamente, las formas farmacéuticas de liberación modificada se pueden diseñar para proporcionar un aumento rápido de la concentración plasmática de la sal de bupropion, la cual aunque puede no permanecer constante, disminuye a una velocidad tal que la concentración plasmática permanece dentro del intervalo terapéutico durante un período de al menos 12 horas y deseablemente de al menos veinticuatro horas.

Las formas farmacéuticas de liberación modificada de la invención se pueden elaborar de muchas formas conocidas

por los técnicos con experiencia en la administración de fármacos y descritas en el estado anterior de la técnica como por ejemplo, "formas farmacéuticas de matriz de liberación modificada", "formas farmacéuticas de matriz de liberación normal" recubiertas con al menos un "recubrimiento de control de la liberación", "formas farmacéuticas osmóticas", "formas farmacéuticas multiparticuladas" y "formas farmacéuticas de retención gástrica". La USP considera que las expresiones liberación controlada, liberación prolongada y liberación sostenida son intercambiables. En consecuencia, las expresiones "liberación modificada", "liberación controlada", "control de la liberación", "liberación controlada por velocidad", "liberación prolongada" y "liberación sostenida" se usan indistintamente aquí. Para la discusión, la definición de la expresión "liberación modificada" abarca el alcance de las definiciones para las expresiones "liberación extendida", "absorción mejorada", "liberación controlada" y "liberación retardada".

"Formas farmacéuticas de liberación controlada" o "formas farmacéuticas con control de la liberación", o formas farmacéuticas que presentan una "liberación controlada" de la sal de bupropion como se usan aquí se definen con el significado de formas farmacéuticas administradas una o dos veces al día que liberan la sal de bupropion a una velocidad controlada y proporcionan concentraciones plasmáticas de la sal de bupropion que permanecen controladas en el tiempo dentro del intervalo terapéutico de la sal de bupropion en un período de 12 ó 24 horas. "Liberación controlada" o "control de la liberación" se definen con el significado de la liberación del fármaco gradualmente o de manera controlada por unidad de tiempo. Por ejemplo, la velocidad controlada puede ser una velocidad constante que proporciona concentraciones plasmáticas de la sal de bupropion que permanecen invariables en el tiempo dentro del intervalo terapéutico de la sal de bupropion en un período de al menos 12 ó 24 horas.

"Formas farmacéuticas de liberación sostenida" o formas farmacéuticas que presentan "liberación sostenida" de la sal de bupropion como se usan aquí se definen con el

significado de formas farmacéuticas que se administran una vez al día que proporcionan una liberación suficiente de la sal de bupropion para proporcionar una dosis terapéutica poco después de la administración y después una liberación gradual durante un período prolongado de tal manera que la forma farmacéutica de liberación sostenida proporcione beneficio terapéutico en un período de 12 ó 24 horas.

"Formas farmacéuticas de liberación sostenida o extendida" o formas farmacéuticas que presentan una "liberación sostenida o extendida" de la sal de bupropion como se usan aquí se definen de modo de incluir las formas farmacéuticas administradas una o dos veces al día que liberan la sal de bupropion lentamente, de modo que las concentraciones plasmáticas de la sal de bupropion se mantienen a un nivel terapéutico durante un período prolongado de tiempo tal que la forma farmacéutica de liberación sostenida o extendida proporciona un beneficio terapéutico en un período de 12 ó 24 horas.

"Formas farmacéuticas de liberación prolongada" o formas farmacéuticas que presentan una "liberación prolongada" de la sal de bupropion como se usan aquí se definen con el significado de formas farmacéuticas administradas una vez al día que mantienen la absorción de la sal de bupropion durante un período más largo que una forma farmacéutica de liberación inmediata o de matriz de liberación normal, sin recubrir, convencionales, y que proporciona beneficio terapéutico durante un período de al menos 12 horas y más característicamente durante un período de al menos 24 horas.

"Formas farmacéuticas de liberación retardada" o formas farmacéuticas que presentan "liberación retardada" de la sal de bupropion como se usan aquí se definen con el significado de formas farmacéuticas que se administran una vez al día que no liberan eficazmente el fármaco inmediatamente después de la administración sino posteriormente. Las formas farmacéuticas de liberación retardada proporcionan una demora en el tiempo antes del comienzo de la absorción del fármaco. 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 fármaco alcance la concentración eficaz mínima.

"Formas farmacéuticas de absorción mejorada" o formas farmacéuticas que presentan una "absorción mejorada" de la sal de bupropion como se usan aquí se definen con el significado de formas farmacéuticas que cuando se exponen a condiciones similares, mostrarán una liberación mayor y/o más absorción de la base de bupropion en comparación con otras formas farmacéuticas con la misma cantidad o mayor cantidad de base de bupropion. Se puede lograr el mismo efecto terapéutico con menos base de bupropion en la forma farmacéutica de absorción mejorada en comparación con otras formas farmacéuticas.

La expresión "matriz de liberación controlada" como se usa aquí se define con el significado de una forma farmacéutica en la que la sal de bupropion y sus combinaciones se dispersan dentro de una matriz, que puede ser soluble o insoluble o una combinación. Las formas farmacéuticas de matriz de liberación controlada del tipo insoluble también se denominan "matrices poliméricas insolubles", "matrices hinchables" o "matrices lipídicas" según los componentes que constituyen la matriz. Las formas farmacéuticas de matriz de liberación controlada del tipo soluble también se denominan "matrices coloidales hidrófilas", "matrices erosionables" o "sistemas de reservorio". Las formas farmacéuticas de matriz de liberación controlada de la invención se refieren a las formas farmacéuticas que comprenden una matriz insoluble, una matriz soluble o una combinación de matrices insolubles y solubles en las cuales la velocidad de liberación es más lenta que la de las formas farmacéuticas sin matriz, sin recubrir, convencionales o de liberación inmediata o las formas farmacéuticas de "matriz de liberación normal" sin recubrir. Las formas farmacéuticas de matriz de liberación controlada se pueden recubrir con un "recubrimiento de control de la liberación" para enlentecer aún más la liberación de la sal de bupropion de la forma farmacéutica de matriz de liberación controlada. Dichas formas farmacéuticas de matriz de liberación controlada, recubiertas, pueden presentar "liberación modificada", "liberación controlada",

"liberación sostenida", "liberación extendida", "liberación prolongada", "liberación retardada" o combinaciones de éstas de la sal de bupropion.

La expresión "matriz de liberación normal" como se usa aquí se define con el significado de formas farmacéuticas en las que la sal de bupropion y sus combinaciones se dispersan dentro de una matriz, que puede ser soluble o insoluble, o combinaciones de éstas pero elaboradas de tal manera que la liberación de la sal de bupropion imita la velocidad de liberación de una forma farmacéutica convencional sin matriz, sin recubrir, o de liberación inmediata que comprende la sal de bupropion. La velocidad de liberación de las formas farmacéuticas de matriz de liberación normal se puede enlentecer o modificar conjuntamente con un "recubrimiento de control de la liberación".

Un "recubrimiento de control de la liberación" o "recubrimiento de liberación controlada" como se usan aquí se definen con el significado de un recubrimiento funcional que puede comprender, por ejemplo, al menos un polímero independiente del pH, un polímero dependiente del pH (como por ejemplo los tipos entéricos o entéricos inversos) un polímero soluble, un polímero insoluble, lípidos, materiales lipídicos o sus combinaciones que cuando se aplica sobre una forma farmacéutica puede enlentecer (por ejemplo cuando se aplica a una forma farmacéutica de matriz de liberación normal), enlentecer aún más (por ejemplo cuando se aplica a una forma farmacéutica de matriz de liberación controlada) o modificar la velocidad de liberación de la sal de bupropion cuando se aplica a una forma farmacéutica sin recubrir. Por ejemplo, el recubrimiento de control de la liberación se puede diseñar de tal manera que cuando dicho recubrimiento de control de la liberación se aplica a una forma farmacéutica, la forma farmacéutica conjuntamente con el recubrimiento de control de la liberación pueden presentar la liberación de la sal de bupropion, por ejemplo, como una "liberación modificada", "liberación controlada", "liberación sostenida", "liberación extendida", "liberación retardada", "liberación prolongada" o sus combinaciones. El "recubrimiento de control de la liberación" puede

comprender opcionalmente otros materiales que pueden alterar la funcionalidad del recubrimiento de control de la liberación.

El término "barrera contra la humedad" como se usa aquí es una barrera que impide o retrasa la absorción de la humedad. Se sabe que las sales de bupropion son higroscópicas y, como tales, son sensibles a la descomposición con el transcurso del tiempo en condiciones de humedad elevada. La proporción de los componentes de la barrera contra la humedad y la cantidad de barrera contra la humedad aplicada opcionalmente sobre el recubrimiento de control de la liberación o sobre el núcleo es típicamente tal que la barrera contra la humedad no está comprendida por la definición y los requisitos de la USP para un recubrimiento entérico. Adecuadamente, la barrera contra la humedad está compuesta de un polímero entérico y/o acrílico, adecuadamente un polímero acrílico, opcionalmente un plastificante y un potenciador de la penetración. El potenciador de la penetración es una sustancia hidrófila, que permite el ingreso de agua sin alteración física del recubrimiento. La barrera contra la humedad puede contener además otros excipientes inertes convencionales, que pueden mejorar el procesamiento de la formulación de liberación extendida descrita aquí.

El término "medicamento" como se usa aquí se refiere a todas las formas farmacéuticas posibles orales y no orales, incluidas pero no exclusivamente, todas las formas farmacéuticas de liberación modificada, los sistemas de liberación controlada por ósmosis, los sistemas de liberación controlada por erosión, los sistemas de liberación controlada por disolución, los sistemas de liberación controlada por difusión, los comprimidos de matriz, los comprimidos con recubrimiento entérico, los comprimidos con recubrimiento simple y doble (incluidos los comprimidos de liberación extendida y de absorción mejorada descritos aquí), las cápsulas, los minicomprimidos, los comprimidos oblongos, las perlas recubiertas, los gránulos, los esferoides, los pelets (gránulos comprimidos), las micropartículas, las suspensiones, las tópicas como las composiciones transdérmicas y transmucosas y los sistemas de

administración (que contienen o no matrices), composiciones inyectables e inhalables.

Las expresiones "estabilidad mejorada", "mayor estabilidad", "estabilidad aumentada" o "más estable" como se usan aquí al referirse a una sal de bupropion (bupropion HBr) significan que la sal de bupropion (bromhidrato de bupropion) y las composiciones, las formulaciones o los medicamentos que contienen la sal de bupropion, cuando se exponen a condiciones similares, es decir, cuando se almacenan durante al menos 3 meses en condiciones de almacenamiento acelerado (40 grados C, 75 % de humedad relativa) y/o cuando se almacenan durante al menos 3, 4, 5 y/o 6 meses o un año o más en condiciones de almacenamiento acelerado (40 grados C, 75 % de humedad relativa) presentan una menor degradación según se determina por una menor formación de al menos un producto de degradación que una composición que contiene bupropion HCl, por lo demás similar. Además la estabilidad mejorada o mayor estabilidad o estabilidad aumentada de una sal de bupropion (en relación con el bupropion HCl) incluye composiciones de bupropion HBr que presentan perfiles de disolución y por consiguiente una concentración más uniformes, en comparación con una formulación de clorhidrato de bupropion, por lo demás similar, después de ser almacenadas durante al menos 3, 4, 5 y/o 6 meses en las mismas condiciones de almacenamiento acelerado de 40 grados C y 75 % de humedad relativa.

"Menos degradación" significa cualquier disminución cuantificable en la cantidad de al menos una impureza característica de la degradación de bupropion o cualquier diferencia cuantificable en la retención de la concentración en relación con una composición de bupropion HCl, por lo demás similar, después de ser almacenadas durante al menos 3, 4, 5 y/o 6 meses o más, p. ej., uno o dos años en las condiciones de almacenamiento acelerado identificadas precedentemente. Los "productos de degradación" incluyen los enumerados en la página 281 de la 26ª edición de la USP y todos los otros productos de degradación que pueden aparecer como picos en un cromatograma durante la determinación del

contenido que son característicos de la degradación de bupropion.

Según se usa aquí "impurezas totales" significa todos los productos de degradación que son resultado de la degradación del bromhidrato de bupropion. Los "productos de degradación" incluyen los enumerados en la página 281 de la 26ª edición de la USP y todos los otros productos de degradación que pueden aparecer como picos en un cromatograma durante la determinación del contenido.

El término "plastificante" como se usa aquí incluye todos los compuestos capaces de plastificar o ablandar un polímero o un aglutinante usados en la presente invención. El uso de plastificantes es opcional y puede estar incluido en la forma farmacéutica para modificar las propiedades y las características de los polímeros usados en el o los recubrimientos o en el núcleo de la forma farmacéutica para el procesamiento conveniente durante la fabricación del o los recubrimientos y/o del núcleo de la forma farmacéutica. Una vez que se prepararon el o los recubrimientos y/o el núcleo, ciertos plastificantes pueden actuar para aumentar la hidrofilicidad del o de los recubrimientos y/o del núcleo de la forma farmacéutica en el ambiente de uso. Durante la fabricación del o los recubrimientos y/o el núcleo, el plastificante puede reducir la temperatura de fusión o la temperatura de transición vítrea (temperatura del punto de ablandamiento) del polímero o aglutinante. Los plastificantes pueden expandir el peso molecular promedio de un polímero en el cual están incluidos disminuyendo de ese modo su temperatura de transición vítrea o punto de ablandamiento. Los plastificantes también pueden reducir la viscosidad de un polímero. Los plastificantes pueden impartir algunas propiedades físicas particularmente ventajosas a las formas farmacéuticas de la invención.

El término "porción" como se usa aquí se define con el significado de la molécula o el ion, con exclusión de las porciones de la molécula agregadas que hacen que el fármaco sea un éster o una sal (incluida una sal con hidrógeno o enlaces de coordinación), responsable de la acción fisiológica o farmacológica del fármaco.

El término "micropartícula", como se usa aquí se refiere a una formulación de un fármaco en forma de partículado discreto y es intercambiable con los términos "microesferas", "partículas esféricas", "microcápsulas", "partículas", "multiparticulados", "gránulos", "esferoides", "perlas" y "pelets".

El término "núcleo" como se usa aquí se define con el significado de cualquier estructura que está rodeada por una pared, una membrana o un recubrimiento. La pared, la membrana o el recubrimiento pueden ser un recubrimiento funcional o no funcional.

El término "comprimido" como se usa aquí se refiere a una única forma farmacéutica, es decir la única entidad que contiene el principio farmacéutico activo que se administra al sujeto. El término "comprimido" también incluye un comprimido que puede ser la combinación de uno o más "minicomprimidos".

El término "ósmosis" como se usa aquí se refiere al flujo de un disolvente a través de una membrana selectivamente permeable de una región de alto potencial disolvente a una región de bajo potencial disolvente. La membrana selectivamente permeable debe ser permeable al disolvente, pero no al soluto, dando lugar a un gradiente de presión a través de la membrana.

Las expresiones "forma farmacéutica osmótica", "dispositivo de administración osmótica", "forma farmacéutica osmótica de liberación modificada" o "forma farmacéutica osmótica de liberación controlada" como se usan aquí se definen con el significado de formas farmacéuticas que dispensan forzadamente toda o parte de la sal de bupropion mediante la presión creada por ósmosis o por una combinación de ósmosis y difusión del líquido al interior de una forma farmacéutica que fuerza a la sal de bupropion a ser dispensada desde la forma farmacéutica osmótica. Las expresiones "forma farmacéutica osmótica", "dispositivo de administración osmótica", "forma farmacéutica osmótica de liberación modificada", o "forma farmacéutica osmótica de liberación controlada" también abarcan dichas formas que se pueden

recubrir con un "recubrimiento de control de la liberación".

Las expresiones "osmoagente", "agente osmótico", "soluto osmóticamente eficaz", "potenciador osmótico", "compuestos osmóticamente eficaces", "solutos osmóticos", o "agentes que embeben líquido osmótico" se usan todas indistintamente y definen cualquier material que aumenta la presión osmótica del núcleo, aumentando, por lo tanto, la presión hidrostática dentro de la forma farmacéutica osmótica. El osmoagente puede ser soluble o hinchable y puede estar total o parcialmente solubilizado. El osmoagente puede ser la sal de bupropion.

La expresión "farmacéuticamente aceptable" significa compatible con el tratamiento de los sujetos, en particular, los seres humanos.

Los términos "sujeto" o "paciente" como se usan aquí significan todos los miembros del reino animal, en particular, los seres humanos.

La expresión "cantidad eficaz" como se usa aquí significa una "cantidad farmacéuticamente eficaz". Una "cantidad farmacéuticamente eficaz" es la cantidad de sal de bupropion o de sus polimorfos o enantiómeros que es suficiente para producir una respuesta biológica apreciable cuando se administra a un paciente. Se apreciará que la dosis terapéutica precisa dependerá de la edad y el estado del paciente y la naturaleza de la afección a ser tratada y será en último término a juicio del médico tratante.

Según se usa aquí, y según se entiende en el área, "tratamiento" es un enfoque para obtener resultados beneficiosos o deseados, incluidos los resultados clínicos. Los resultados clínicos beneficiosos o deseados pueden incluir, pero no exclusivamente, el alivio o la mejoría de uno o más síntomas o afecciones, la reducción del alcance de la enfermedad, la estabilización (es decir no empeoramiento) del estado de la enfermedad, la prevención de la propagación de la enfermedad, el retraso o enlentecimiento del empeoramiento de la enfermedad, la mejoría o paliación del estado de la enfermedad y la

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remisión (ya sea parcial o total), ya sean detectables o no detectables. "Tratamiento" también puede significar prolongar la supervivencia en comparación con la supervivencia esperada si no se recibe tratamiento.

"Paliar" una enfermedad o un trastorno significa que el grado y/o las manifestaciones clínicas indeseables de un trastorno o una enfermedad se reducen y/o el tiempo que lleva el empeoramiento de la enfermedad se enlentece o se alarga, en comparación con el trastorno sin tratar.

Los términos "un" o "una" como se usan aquí significan "uno/a" o "uno/a o más".

Las expresiones "alrededor de" o "aproximadamente" como se usan aquí significan dentro de un intervalo de error aceptable para el valor particular determinado por un técnico con experiencia en el tema, que dependerá en parte de cómo se mide o determina el valor, es decir, de las limitaciones del sistema de medición. Por ejemplo, "alrededor de" puede significar dentro de 1 o más de 1 desviaciones estándar, según la práctica en el área. Donde se describen valores particulares en la solicitud y las reivindicaciones, a menos que se indique lo contrario, el término "alrededor de" significa dentro de un intervalo de error aceptable para el valor particular.

A menos que se indique lo contrario, se entenderá que todos los números que expresan cantidades de ingredientes, propiedades como el peso molecular, condiciones de reacción y demás, usados en la especificación y las reivindicaciones son modificados en todos los casos por la expresión "alrededor de". En consecuencia, a menos que se indique lo contrario, los parámetros numéricos establecidos en la siguiente especificación y las reivindicaciones adjuntas son aproximaciones que pueden variar según las propiedades deseadas que se busca obtener mediante la presente invención. Como mínimo, y no como un intento por limitar la aplicación de la doctrina de equivalentes al alcance de las reivindicaciones, cada parámetro numérico se debe interpretar al menos considerando el número de dígitos significativos informados y aplicando las técnicas de redondeo comunes.

Otros términos se definen según aparecen en la descripción siguiente y se deben interpretar en el contexto en el cual aparecen.

DESCRIPCIÓN DETALLADA

Existe la necesidad de formas farmacéuticas que comprendan una sal farmacéuticamente aceptable de bupropion, que sean más estables que composiciones, por lo demás similares, que contienen clorhidrato de bupropion. En consecuencia, la presente invención se relaciona con formas farmacéuticas que contienen una cantidad eficaz de bromhidrato de bupropion que son más estables que el clorhidrato de bupropion. Además, la invención abarca sus polimorfos y formas enantioméricas purificadas específicas. La presente invención también se relaciona con el uso de tales formas farmacéuticas para el tratamiento de una o más afecciones en un sujeto adecuadas para el tratamiento con bupropion o sus sales farmacéuticamente aceptables, como la depresión, la obesidad, el abandono del hábito de fumar y otras afecciones tratables con bupropion como se divulga aquí.

Formulaciones

La presente invención abarca cualquier medicamento que contenga una cantidad farmacéuticamente eficaz de una sal de bupropion estable de acuerdo con la invención, es decir, bromhidrato de bupropion. Esto incluye medicamentos administrables tanto por vía oral como no oral como medicamentos tópicos, inyectables, aerosoles y otros medicamentos inhalables. En particular dichas composiciones de medicamentos incluyen formas farmacéuticas de liberación modificada administrables por vía oral que contienen la sal de bupropion. Las dosis se pueden presentar de manera conveniente en formas farmacéuticas unitarias y se pueden preparar por cualquiera de los métodos conocidos en el área farmacéutica.

"Forma farmacéutica" como se usa aquí, significa una preparación farmacéutica que comprende una cantidad eficaz de una sal de bupropion que es más estable que el clorhidrato de bupropion. En al menos una realización la sal de bupropion es bromhidrato de bupropion.

Una "forma farmacéutica sólida" como se usa aquí, significa una forma farmacéutica que no es ni líquida ni gaseosa. Las formas farmacéuticas incluyen formas farmacéuticas sólidas, como comprimidos, polvos, micropartículas, cápsulas, supositorios, sobres, trociscos, parches y pastillas así como suspensiones líquidas y elixires. Las cápsulas contienen la composición sólida dentro de una cápsula que puede hacerse de gelatina u otro material de encapsulado convencional.

Las formas farmacéuticas de liberación modificada contempladas en la presente invención pueden ser multiparticuladas o monolíticas. Por ejemplo, los técnicos con experiencia en el área farmacéutica y el diseño de medicamentos están al tanto de las matrices de liberación modificada convencionalmente usadas en las composiciones farmacéuticas orales adoptadas para la liberación modificada y de los medios para su preparación. Ejemplos de formulaciones de liberación modificada se divulgan en las Patentes de los Estados Unidos 5,591,452 y 5,965,161.

Una formulación de liberación modificada que contiene la sal de bupropion de acuerdo con la presente invención se puede recubrir con uno o más recubrimientos funcionales o no funcionales. Los ejemplos de recubrimientos funcionales incluyen recubrimientos poliméricos de liberación controlada (es decir recubrimientos de liberación controlada), recubrimientos de barrera contra la humedad, recubrimientos poliméricos entéricos y similares. Los recubrimientos no funcionales son recubrimientos que no afectan a la liberación de fármacos, pero que afectan a otras propiedades; como la mejora de las características de estabilidad químicas, biológicas o físicas, o la mejora del aspecto físico de la formulación.

En al menos una realización de la presente invención el recubrimiento polimérico de liberación controlada (o recubrimiento de control de la liberación) comprende un polímero acrílico. Los polímeros acrílicos adecuados incluyen, pero no exclusivamente, copolímeros del ácido

acrílico y el ácido metacrílico, copolímeros de metacrilato de metilo, metacrilatos de etoxietilo, metacrilato de cianoetilo, copolímero de metacrilato de aminoalquilo, poli(ácido acrílico), poli(ácido metacrílico), copolímero de ácido metacrílico alquilamina, poli(metacrilato de metilo), poli(ácido metacrílico) (anhídrido), poliacrilamida, poli(anhídrido del ácido metacrílico) y copolímeros de metacrilato de glicidilo.

En al menos una realización se emplean compuestos de amonio cuaternario polimerizables en el recubrimiento de control de la liberación, de los cuales los ejemplos no limitantes incluyen ésteres aminoalquílicos y aminoalquilamidas cuaternizados del ácido acrílico y el ácido metacrílico, por ejemplo metosulfato de β-metacril-oxietil-trimetil-amonio, cloruro de β-acriloxi-propil-trimetil-amonio y metosulfato de trimetilaminometil-metacrilamida. El átomo de amonio cuaternario también puede formar parte de un heterociclo, como en el cloruro de metacriloxietilmetil-morfolinio o la correspondiente sal de piperidinio, o se puede unir a un grupo ácido acrílico o a un grupo ácido metacrílico a través de un grupo que contiene heteroátomos, como un grupo éter poliglicólico. Otros compuestos de amonio cuaternario polimerizables adecuados incluyen heterociclos de nitrógeno cuaternizados sustituidos con vinilo como las sales de metilvinil piridinio, los ésteres de vinilo de ácidos amino carboxílicos cuaternizados, las sales de estiriltrialquilamonio y similares. Otros compuestos de amonio cuaternario polimerizables útiles en la presente invención incluyen cloruro y metosulfato de acril- y metacril-oxietiltrimetilamonio, cloruro de bencildimetilamoniometil-metacrilato, metosulfato de dietilmetilamoniometil-acrilato y -metacrilato, cloruro de N-trimetilamoniopropilmetacrilamida y cloruro de N-trimetilamonio-2,2-dimetilpropil-1-metacrilato.

En al menos una realización el polímero acrílico está compuesto de uno o más copolímeros de metacrilato de amonio. Los copolímeros de metacrilato de amonio (como los que se comercializan bajo la marca registrada Eudragit® RS y RL) se describen en el National Formulary (NF) XVII como copolímeros totalmente polimerizados de

ésteres de ácido acrílico y metacrílico con un contenido bajo de grupos amonio cuaternario. Para obtener un perfil de disolución deseado para un principio terapéuticamente activo dado, como bromhidrato de bupropion, se pueden incorporar dos o más copolímeros de metacrilato de amonio con diferentes propiedades físicas. Por ejemplo, se sabe que cambiando la relación molar entre los grupos de amonio cuaternario y los ésteres (met)acrílicos neutros, se pueden modificar las propiedades de permeabilidad del recubrimiento resultante.

En otras realizaciones de la presente invención, el recubrimiento de control de la liberación incluye además un polímero cuya permeabilidad es dependiente del pH, como los polímeros aniónicos sintetizados a partir del ácido metacrílico y el éster metílico del ácido metacrílico. Dichos polímeros son comercializados, por ejemplo, por Rohm Pharma GmbH con el nombre comercial Eudragit® L y Eudragit® S. Se sabe que la relación entre los grupos carbóxilo libre y los ésteres es 1:1 en Eudragit® L y 1:2 en Eudragit® S. Eudragit® L es insoluble en ácidos y agua pura, pero se torna cada vez más permeable por encima de pH 5,0. Eudragit® S es similar, excepto porque se torna cada vez más permeable por encima de pH 7. Los recubrimientos de polímero acrílico hidrófobos también pueden incluir un polímero que tenga carácter catiónico a base de metacrilato de dimetilaminoetilo y ésteres del ácido metacrílico neutros (como Eudragit® E, comercializado por Rohm Pharma). Los recubrimientos de polímero acrílico hidrofóbos de la presente invención pueden incluir además un copolímero neutro a base de poli(met)acrilatos, como Eudragit® NE (NE = éster neutro), comercializado por Rohm Pharma. Las películas de laca de Eudragit® NE 30D son insolubles en agua y líquidos digestivos, pero permeables e hinchables.

En al menos otra realización de la invención, el recubrimiento de control de la liberación comprende una dispersión de poli(etilacrilato, metacrilato de metilo) 2:1 (Kollicoat® EMM 30D, BASF).

En al menos otra realización de la invención, el recubrimiento de control de la liberación comprende un acetato de polivinilo estabilizado con

polivinilpirrolidona y lauril sulfato de sodio como Kollicoat® SR30D (BASF). El perfil de disolución se puede alterar cambiando las cantidades relativas de diferentes lacas de resina acrílica incluidas en el recubrimiento. También, cambiando la relación molar entre el agente polimerizable que mejora la permeabilidad (por ejemplo, los compuestos de amonio cuaternario) y los ésteres (met)acrílicos neutros, se pueden modificar las propiedades de permeabilidad (y por lo tanto el perfil de disolución) del recubrimiento resultante.

En al menos una realización de la invención el recubrimiento de control de la liberación comprende etilcelulosa, que se puede usar como un polímero seco (como Ethocel®, Dow Corning) solubilizado en disolvente orgánico antes de usar, o como una dispersión acuosa. Una dispersión acuosa de etilcelulosa adecuada comercialmente disponible es Aquacoat® (FMC Corp., Filadelfia, Pa., EE.UU.). El Aquacoat® se puede preparar disolviendo la etilcelulosa en un disolvente orgánico inmiscible con agua y luego emulsionar el mismo en agua en presencia de un tensioactivo y un estabilizador. Después de la homogeneización para generar gotitas submicrónicas, el disolvente orgánico se evapora al vacío para formar un pseudolátex. El plastificante no se incorpora en el pseudolátex durante la fase de fabricación. Por lo tanto, antes de usar el mismo como un recubrimiento, se puede mezclar el Aquacoat® íntimamente con un plastificante adecuado. Otra dispersión acuosa adecuada de etilcelulosa se comercializa como Surelease® (Colorcon, Inc., West Point, Pa., EE.UU.). Este producto se puede preparar incorporando un plastificante en la dispersión durante el proceso de fabricación. Se prepara una colada caliente de un polímero, un plastificante (por ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, ácido oleico) como una mezcla homogénea, que luego se diluye con una solución alcalina para obtener una dispersión acuosa que se puede aplicar directamente sobre los sustratos.

Otros ejemplos de polímeros que se pueden usar en el recubrimiento de control de la liberación incluyen ftalato acetato de celulosa, trimaleato acetato de celulosa, ftalato de hidroxipropilmetilcelulosa, ftalato acetato de polivinilo, ftalato de alcohol polivinílico,

laca; hidrogeles y materiales que forman geles, como polímeros carboxivinílicos, alginato de sodio, carmelosa de sodio, carmelosa de calcio, carboximetil almidón sódico, alcohol polivínílico, hidroxietilcelulosa, metilcelulosa, etilcelulosa, gelatina, almidón y polímeros reticulados a base de celulosa en los que el grado de reticulación es bajo para facilitar la adsorción de agua y la expansión de la matriz del polímero, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, almidón reticulado, celulosa microcristalina, quitina, pullulan, colágeno, caseína, agar, goma arábiga, carboximetilcelulosa sódica, (polímeros hidrófilos hinchables) poli(hidroxialquilmetacrilato) (peso molecular de 5 k a 5.000 k), polivinilpirrolidona (peso molecular de 10 k a 360 k), hidrogeles aniónicos y catiónicos, zeína, poliamidas, alcohol polivinílico con bajo contenido de acetato residual, una mezcla hinchable de agar y carboximetilcelulosa, copolímeros de anhídrido maleico y estireno, etileno, propileno o isobutileno, pectina (peso molecular 30 k a 300 k), polisacáridos como agar, acacia, karaya, tragacanto, alginas y guar, poliacrilamidas, óxidos de polietileno Polyox® (peso molecular de 100 k a 5.000 k), polímeros de acrilato AquaKeep®, diésteres de poliglucano, alcohol polivinílico y poli N-vinil-2-pirrolidona reticulados, polímeros hidrófilos como los polisacáridos, metilcelulosa, carboximetilcelulosa de sodio o de calcio, hidroxipropilmetilcelulosa, hidroxipropilcelulosa, hidroxietilcelulosa, nitrocelulosa, carboximetilcelulosa, éteres de celulosa, metiletilcelulosa, etilhidroxietilcelulosa, acetato de celulosa, butirato de celulosa, propinionato de celulosa, gelatina, almidón, maltodextrina, pullulan, polivinilpirrolidona, alcohol polivinílico, acetato de polivinilo, ésteres de ácidos grasos de glicerol, poliacrilamida, ácido poliacrílico, gomas naturales, lecitinas, pectina, alginatos, alginato de amonio, alginatos de sodio, calcio y potasio, alginato de propilenglicol, agar y gomas como arábiga, karaya, de algarrobo, tragacanto, carrageninas, guar, xantano, escleroglucano y sus mezclas y combinaciones.

En al menos una realización de la invención las formas farmacéuticas se recubren con polímeros para facilitar la

adhesión a la mucosa del aparato digestivo. Ejemplos no limitantes de polímeros que se pueden usar para la adhesión a la mucosa incluyen carboximetilcelulosa, ácido poliacrílico, Carbopol™, Polycarbophil™, gelatina y otros polímeros naturales o sintéticos.

En al menos una realización de la invención, la forma farmacéutica es un comprimido de liberación extendida que comprende: (i) un núcleo que incluye bromhidrato de bupropion (por ejemplo, de 40 % a 99 % en peso del peso seco del comprimido), un aglutinante como el alcohol polivinílico (por ejemplo, de 0,5 % a 25 % en peso del peso seco del comprimido) y un lubricante como el behenato de glicerilo (por ejemplo, de 0,1 % a 5 % en peso del peso seco del comprimido); y (ii) un recubrimiento de control de la liberación que incluye un polímero formador de película insoluble en agua y permeable al agua como etilcelulosa (por ejemplo, de 1 % a 12 % en peso del peso seco del comprimido), un polímero soluble en agua como polivinilpirrolidona (Povidona® USP), (por ejemplo, de 1,5 % a 10 % en peso del peso seco del comprimido), opcionalmente un plastificante como sebacato de dibutilo, el polietilenglicol 4000 o una mezcla de éstos (por ejemplo, de 0,5 % a 4 % en peso del peso seco del comprimido) y opcionalmente una cera como la cera carnauba (por ejemplo, de 0,01 % a 0,05 % en peso del peso seco del comprimido).

En al menos una realización de la invención, la forma farmacéutica es un comprimido XL de 174 mg que comprende: (i) un núcleo que incluye bromhidrato de bupropion (por ejemplo, 81 % en peso del peso seco del comprimido), un aglutinante como el alcohol polivinílico (por ejemplo, 3 % en peso del peso seco del comprimido) y un lubricante como el behenato de glicerilo (por ejemplo, 3 % en peso del peso seco del comprimido); y (ii) un recubrimiento de control de la liberación que incluye un polímero formador de película, insoluble en agua y permeable al agua como etilcelulosa (por ejemplo, 8 % en peso del peso seco del comprimido), un polímero soluble en agua como polivinilpirrolidona (Povidona® USP), (por ejemplo, 5 % en peso del peso seco del comprimido), opcionalmente un plastificante como sebacato de dibutilo, polietilenglicol 4000 o una mezcla (por ejemplo, 3 % en peso del peso seco

del comprimido) y opcionalmente una cera como cera carnauba (por ejemplo, 0,03 % en peso del peso seco del comprimido).

En al menos una realización de la invención, la forma farmacéutica es un comprimido XL de 348 mg que comprende: (i) un núcleo que incluye bromhidrato de bupropion (por ejemplo, 87 % en peso del peso seco del comprimido), un aglutinante como el alcohol polivinílico (por ejemplo, 3 % en peso del peso seco del comprimido) y un lubricante como el behenato de glicerilo (por ejemplo, 3 % en peso del peso seco del comprimido); y (ii) un recubrimiento de control de la liberación que incluye un polímero formador de película, insoluble en agua y permeable al agua como etilcelulosa (por ejemplo, 4 % en peso del peso seco del comprimido), un polímero soluble en agua como polivinilpirrolidona (Povidona® USP), (por ejemplo, 3 % en peso del peso seco del comprimido), opcionalmente un plastificante como sebacato de dibutilo, polietilenglicol 4000 o una mezcla de éstos (por ejemplo, 2 % en peso del peso seco del comprimido) y opcionalmente una cera como cera carnauba (por ejemplo, 0,01 % en peso del peso seco del comprimido).

Además de las formas farmacéuticas de liberación modificada descritas aquí, se pueden usar otras tecnologías de liberación modificada conocidas por los técnicos con experiencia para lograr las formulaciones de liberación modificada de la presente invención, es decir, formulaciones que proporcionan una $T_{máx}$ media del fármaco y/o otros parámetros farmacocinéticos descritos aquí cuando se administran por ejemplo, por vía oral o por otra vía de administración a los pacientes humanos. Dichas formulaciones se pueden fabricar como una formulación oral de liberación modificada en un comprimido adecuado o una formulación multiparticulada conocida por los técnicos con experiencia en el tema. En cualquier caso, la forma farmacéutica de liberación modificada puede incluir opcionalmente un vehículo de liberación controlada que se incorpora en una matriz junto con el fármaco o que se aplica como un recubrimiento de liberación controlada.

Comprimidos

En otro aspecto específico de la la presente invención, se proporciona un comprimido de liberación modificada que tiene un núcleo que comprende una sal farmacéuticamente aceptable de bupropion y excipientes convencionales, donde la sal de bupropion es más estable que el clorhidrato de bupropion (bromhidrato de bupropion). El núcleo se puede rodear con un recubrimiento de control de la liberación que controla la liberación de la sal de núcleo. En otras realizaciones, se puede agregar opcionalmente una barrera contra la humedad para rodear el recubrimiento de control de la liberación. Esta barrera contra la humedad es opcional dada la estabilidad mejorada del bupropion HBr con relación al bupropion HCl y por selección de recubrimientos con control de la liberación apropiados y de cantidades de éstos. Si está presente, esta barrera contra la humedad puede afectar a la liberación de fármacos in vitro así como evitar que la humedad entre en contacto con la sal de buropion. Opcionalmente, este comprimido puede comprender además uno o más recubrimientos funcionales o no funcionales adicionales alrededor del núcleo, la barrera contra la humedad y/o el recubrimiento de control de la liberación.

Comprimidos (XL) de liberación prolongada

En otro aspecto específico de la presente invención, se proporciona un comprimido (XL) de liberación extendida que tiene un núcleo que comprende una sal farmacéuticamente aceptable de bupropion y excipientes convencionales, en el que la sal de bupropion es más estable que el clorhidrato de bupropion. En al menos una realización la sal de bupropion es bromhidrato de bupropion. El núcleo se puede rodear con un recubrimiento de control de la liberación, que controla la liberación de la sal de bupropion. El comprimido puede comprender opcionalmente uno o más recubrimientos funcionales o no funcionales adicionales alrededor del núcleo o el recubrimiento de control de la liberación. El comprimido de liberación extendida de la invención tiene una inesperada estabilidad mejorada.

El núcleo XL

El núcleo del comprimido de liberación extendida comprende una cantidad eficaz de una sal de bupropion, un

aglutinante y un lubricante y puede contener otros excipientes inertes convencionales. En al menos una realización la sal de bupropion es bromhidrato de bupropion. La cantidad de sal de bupropion presente en el núcleo XL puede variar en una cantidad entre 40 % y 99 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones el bromhidrato de bupropion está presente en una cantidad entre 70 % y 95 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones, el núcleo de la forma farmacéutica de la presente invención comprende bromhidrato de bupropion en una proporción de 40 %, 45 %, 50 %, 55 %, 60 %, 65 %, 70 %, 75 %, 80 %, 85 %, 90 %, 95 % o 99 % del peso seco del nucleo. El comprimido comprende una cantidad eficaz de sal de bupropion que variará típicamente de 50 mg a 450 mg. Por ejemplo, en ciertas realizaciones, el comprimido comprende 174 mg de bromhidrato de bupropion y en otras realizaciones el comprimido comprende 348 mg de bromhidrato de bupropion. En al menos una realización de un comprimido de 174 mg de dosis, el bromhidrato de bupropion está presente entre 75 % y 85 % en peso del peso seco del comprimido. En al menos una realización de un comprimido de 348 mg de dosis, la cantidad de bromhidrato de bupropion puede estar presente entre 80 % y 90 % en peso del peso seco del comprimido. En ciertas realizaciones de los comprimidos de bromhidrato de bupropion de liberación extendida de la invención tanto de 174 mg como de 348 mg de dosis, la cantidad de bromhidrato de bupropion presente es de 90 % a 99 % en peso del núcleo seco para cada dosis.

Se puede agregar un aglutinante (también denominado a veces adhesivo) a una mezcla de relleno y fármaco para aumentar la fuerza mecánica de los gránulos y los comprimidos durante la formación. Los aglutinantes se pueden agregar a la formulación de diferentes maneras: (1) como un polvo seco, que se mezcla con otros ingredientes antes de la aglomeración húmeda, (2) como una solución, que se usa como líquido de aglomeración durante la aglomeración húmeda, y se denomina solución aglutinante, y (3) como un polvo seco, que se mezcla con los otros ingredientes antes de la compactación. En esta forma el aglutinante se denomina aglutinante seco. Las soluciones aglutinantes son una manera común de

incorporar un aglutinante a los gránulos. En ciertas realizaciones, el aglutinante usado en los comprimidos XL está en forma de una solución aglutinante. Ejemplos no limitantes de aglutinantes útiles para el núcleo incluyen aceite vegetal hidrogenado, aceite de ricino, parafina, alcoholes alifáticos superiores, ácidos alifáticos superiores, ácidos grasos de cadena larga, ésteres de ácidos grasos, materiales similares a cera como alcoholes grasos, ésteres de ácidos grasos, glicéridos de ácidos grasos, grasas hidrogenadas, hidrocarburos, ceras normales, ácido esteárico, alcohol estearílico, polímeros hidrófobos e hidrófilos que tienen esqueletos hidrocarbonados y sus mezclas. Ejemplos específicos de polímeros aglutinantes solubles en agua incluyen almidón modificado, gelatina, polivinilpirrolidona, derivados de celulosa (como por ejemplo hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa (HPC)), alcohol polivinílico y sus mezclas. La cantidad de aglutinante presente puede variar de 0,5 % a 25 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones el aglutinante está presente en una cantidad entre 0,5 % y 15 % en peso del peso seco del comprimido; en otras realizaciones entre 1 % y 6 % en peso del peso seco del comprimido; y aún en otras realizaciones en 3 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones tanto de los comprimidos de 174 mg como los de 348 mg de dosis, el aglutinante está presente en una cantidad entre 1 % y 6 % en peso del peso de cada núcleo seco, y en otras realizaciones en 3 % en peso del peso de cada núcleo seco. En al menos una realización de la invención el aglutinante es el alcohol polivinílico.

Se pueden agregar lubricantes a las formulaciones farmacéuticas para reducir cualquier fricción que ocurra entre el sólido y la pared de la matriz durante la fabricación de comprimidos. Una fricción elevada durante la compresión puede causar una serie de problemas, entre otros una inadecuada calidad del comprimido (decapado o incluso fragmentación de comprimidos durante la expulsión y rayones verticales en los bordes del comprimido) y puede incluso detener la producción. En consecuencia, se agregan lubricantes a ciertas formulaciones de comprimidos de la presente invención incluidas ciertas

realizaciones de la formulación XL de comprimidos descrita aquí. Ejemplos no limitantes de lubricantes útiles para el núcleo incluyen behenato de glicerilo, ácido esteárico, aceites vegetales hidrogenados (como aceite de semilla de algodón hidrogenado (Sterotex®), aceite de soja hidrogenado (Sterotex® HM) y aceite de soja hidrogenado y cera de ricino (Sterotex® K), alcohol estearílico, leucina, polietilenglicol (PM 1.450, adecuadamente 4.000 y mayor), estearato de magnesio, monoestearato de glicerilo, ácido esteárico, polietilenglicol, polímeros de óxido de etileno (por ejemplo, los disponibles bajo la marca registrada Carbowax® de Union Carbide, Inc., Danbury, Conn.), lauril sulfato de sodio, lauril sulfato de magnesio, oleato de sodio, estearil fumarato de sodio, DL-leucina, sílice coloidal, sus mezclas y otros conocidos en el área. En al menos una realización de la presente invención, el lubricante es behenato de glicerilo (por ejemplo, Compritol® 888). La cantidad de lubricante presente puede variar de 0,1 % a 6 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones la cantidad de lubricante presente es de 2 % a 3 % en peso del peso seco del comprimido; y en otras realizaciones la cantidad de lubricante presente es 3 % en peso del peso seco del comprimido. En ciertas realizaciones de los comprimidos XL de la invención de 174 mg y 348 mg de dosis, el lubricante está presente en una cantidad de 3 % en peso del peso seco del comprimido, o de 1 % a 6 % en peso del peso seco del núcleo. Por ejemplo, en ciertas realizaciones el lubricante está presente en una cantidad de 3 % en peso del peso seco del núcleo tanto para los comprimidos XL de 174 mg como los de 348 mg de dosis.

En esta etapa, la formulación del núcleo XL de ciertas realizaciones de la presente invención, es una formulación de liberación inmediata sin recubrimiento que da lugar a una disolución de 100 % de la sal de bupropion en el transcurso de 1 hora. En al menos una realización el núcleo XL es una formulación de matriz de liberación normal. En ciertas realizaciones el núcleo comprende una cantidad farmacéuticamente eficaz de bromhidrato de bupropion, un aglutinante (por ejemplo, alcohol polivinílico) y un lubricante (por ejemplo, behenato de glicerilo). Otros excipientes inertes compatibles con los

objetivos de la invención también se pueden agregar a la formulación del núcleo. Los excipientes inertes adicionales se pueden agregar para facilitar la preparación y/o mejorar la aceptación por parte del paciente de la forma farmacéutica de liberación extendida final según se describe aquí. Los excipientes inertes adicionales son bien conocidos por los técnicos con experiencia y se pueden encontrar en la bibliografía pertinente, por ejemplo en el Handbook of Pharmaceutical Excipients. Ejemplos no limitantes de tales excipientes incluyen lactosa secada por aspersión, sorbitol, manitol y cualquier derivado de celulosa.

En al menos una realización de la invención, los gránulos que se van a comprimir para formar el núcleo del comprimido XL de la invención descrito aquí, se fabrican mediante el proceso de granulación húmeda. La granulación húmeda implica la agitación de un polvo (el fármaco activo) por convención en presencia de un líquido (la solución aglutinante) seguida de secado. Para formar los gránulos, que al final se van a comprimir en forma de núcleos de los comprimidos, primero se granula la sal de bupropion, por ejemplo, con una solución 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 aglutinante (por ejemplo, alcohol polivinílico) se disuelve o se dispersa primero en un disolvente adecuado (por ejemplo, agua). Luego se pulveriza en la parte superior la solución aglutinante sobre el fármaco en un granulador (p. ej., un granulador de lecho fluidizado). Alternativamente, la granulación también se puede llevar a cabo en un mezclador convencional o de alto cizallamiento. Si fuera necesario, se pueden mezclar excipientes inertes adicionales (p. ej., un relleno) con la sal de bupropion antes del paso de granulación.

Posteriormente se secan los gránulos formados y luego se tamizan antes de mezclar dichos gránulos con el lubricante. En ciertas realizaciones, los gránulos secos se tamizan a través de un tamiz de malla de 1,4 mm. Los gránulos tamizados se mezclan luego con el lubricante, y si fuera necesario, con cualquier otro excipiente inerte

adicional, que pueda mejorar el procesamiento de los comprimidos de liberación extendida de la invención. La mezcla de los gránulos con el lubricante y si fuera necesario, con cualquier otro excipiente inerte, como por ejemplo un deslizante, se puede llevar a cabo en un mezclador en V u otro aparato de mezcla adecuado. Los deslizantes pueden mejorar la capacidad de fluir del polvo. Esto es especialmente importante durante la producción de comprimidos a velocidades altas de producción y durante la compactación directa. Sin embargo, debido a que el flujo adecuado requerido es un flujo alto, a menudo también se agrega un deslizante a la granulación antes de la formación de comprimidos. Posteriormente los gránulos mezclados se comprimen en forma de comprimidos y de aquí en adelante se denominan núcleos de los comprimidos. Los núcleos de los comprimidos se pueden obtener mediante el uso de técnicas y equipo corrientes bien conocidos por los técnicos con experiencia. Por ejemplo, los núcleos de los comprimidos XL se pueden obtener con una compresora rotatoria (también denominada compresora multiestación) equipada con punzones adecuados.

Los gránulos también se pueden preparar usando otros procesos conocidos por los técnicos con experiencia. Los ejemplos de otros procesos de fabricación de gránulos incluyen granulación seca (por ejemplo, aglutinación, compactación con rodillos), compresión directa, extrusión, esferonización, granulación por fusión y granulación rotatoria.

Un ejemplo del proceso de granulación para los núcleos XL (lote 60 kg) es el siguiente: Se usa un procesador de lecho fluidizado para la granulación a fin de aglomerar las partículas de los materiales para obtener un tamaño de partícula uniforme para la mezcla final. La solución de granulación se prepara por disolución del aglutinante (p. ej., alcohol polivinílico) en agua purificada caliente mientras se mezcla. Se puede ajustar el contenido porcentual de sólidos para obtener una viscosidad que permita controlar la acumulación (tamaño de aglomeración) del material. Una viscosidad menor conduce a partículas más pequeñas y una viscosidad mayor conduce a partículas más grandes. Además la velocidad de

aplicación (p. ej. de 150 g/min a 250 g/min; o 200 g/min), la posición de la pistola de pulverización (p. ej. en la posición central) y el tamaño de la boquilla (p. ej. de 0,5 mm a 2 mm; o 1 mm) y la presión de pulverización (p. ej. de 20 psi a 40 psi; o 30 psi) contribuyen a controlar el tamaño de partícula. El material activo se fluidiza y se calienta (p. ej., de 35°C a 45°C; o 40°C) antes de comenzar a aplicar la solución. Durante el ciclo de pulverización, la temperatura del lecho (por ejemplo, de 35°C a 45°C; o 40°C) se mantiene constante para evitar la humectación en exceso. Una vez que se aplica toda la solución aglutinante necesaria, el material se seca adicionalmente hasta el valor de LOD (es decir pérdida por secado, por sus siglas en inglés) buscado (por ejemplo, por debajo de 1 %) antes de la descarga. La cantidad de aglutinante (por ejemplo, alcohol polivinílico) es entre 2 % y 6 % y en algunos casos 3 %; y la concentración de la solución es entre 3 % y 7 %, y en algunos casos 4,5 %. El tiempo del proceso de aglomeración para el lote de 60 kg es entre 45 minutos y 220 minutos y en algunos casos de 150 minutos. Una vez que el granulado está seco, el material se pasa a través de un tamiz de 1,4 y 2,00 mm para separar todas las partículas de mayor tamaño. Las partículas de mayor tamaño se pasan por el molino para reducirlas. Las partículas de mayor tamaño en general no exceden el 5 % de la producción total. Los materiales tamizados y molidos se colocan en un mezclador de cilindros (por ejemplo, un mezclador en V o un mezclador de tolva) y se agrega el lubricante (por ejemplo, behenato de glicerilo). El lubricante se tamiza y se agrega a los gránulos y se mezcla al número predeterminado de revoluciones o tiempo (por ejemplo, tiempo de mezcla de 5 min a 15 min y en algunos casos 10 min). El porcentaje de lubricante es entre 0,5 % y 4 %, y en algunos casos de 2 %. El nivel de lubricación se establece para una cobertura suficiente de la distribución de tamaño de partícula ya sea más grande o más pequeña. Otras características incluyen la densidad aparente (por ejemplo, de 0,3 g/ml a 0,8 g/ml y en algunos casos 0,5 g/ml), y el contenido de humedad (por ejemplo, no más de 1 %). El tamaño de partícula y el flujo de la mezcla final son factores para obtener un llenado uniforme de las cavidades en una compresora

rotatoria. El flujo y la velocidad de rotación máxima de la prensa se ajustan (dependiendo del tipo/tamaño 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 través de un embudo a un dispositivo distribuidor para llenar las cavidades de la matriz que pasan por debajo de dicho dispositivo. Se hacen ajustes de peso para mantener el peso dentro del rango especificado, y se hacen ajustes a la regulación 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 0,5 %) del comprimido. Un espesor adecuado (con relación al área superficial total) y una menor friabilidad ayudan a reducir el daño del núcleo y la pérdida de principio activo durante el recubrimiento. Se toman muestras de los comprimido a intervalos predeterminados para controlar las especificaciones.

Recubrimientos

Los núcleos de los comprimidos se pueden recubrir para la administración a un sujeto. En al menos una realización de la invención, los núcleos de los comprimidos se recubren con un recubrimiento de control de la liberación de liberación extendida ("Recubrimiento de control de la liberación XL"). En al menos otra realización, los núcleos de los comprimidos se recubren con un recubrimiento acuoso con control de la liberación que comprende una dispersión acuosa de un copolímero de éster neutro sin ningún grupo funcional ("Recubrimiento de control de la liberación AQ").

En ciertas realizaciones la forma farmacéutica comprimido comprende una barrera contra la humedad opcional además del recubrimiento de control de la liberación. El recubrimiento de control de la liberación y la barrera contra la humedad se pueden aplicar en dos etapas. El recubrimiento de control de la liberación se puede aplicar directamente sobre la superficie de los núcleos de los comprimidos y actúa controlando la liberación de la sal de bupropion. La barrera contra la humedad se puede aplicar directamente sobre la superficie del recubrimiento de control de la liberación para impedir o retrasar la absorción de humedad.

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A continuación se proporcionan ejemplos proféticos de las formulaciones del recubrimiento de control de la liberación. Se debe entender que los constituyentes y/o las proporciones de los constituyentes en estos recubrimientos así como las cantidades de éstos se pueden variar para lograr formulaciones que posean diferentes características de liberación. En todos los casos en los que se proporcionan ejemplos proféticos estas composiciones están destinadas a ser ejemplos y se debe comprender que los procedimientos, los constituyentes, sus cantidades y similares específicos, se pueden variar para obtener una composición que posea las propiedades deseadas.

En al menos una realización el recubrimiento de control de la liberación es una formulación de recubrimiento de liberación retardada para un núcleo de un comprimido, la formulación de recubrimiento que se va a aplicar al núcleo comprende:

Eudragit L12.5	50 % en peso de la suspensión de recubrimiento
Citrato de trietilo	0,63 % en peso de la suspensión de recubrimiento
Talco	1,25 % en peso de la suspensión de recubrimiento
Alcohol isopropílico	48,12 % en peso de la suspensión de recubrimiento

Sólidos totales = 8,1 %
Contenido del polímero de la suspensión = 6,3 %
La preparación de la formulación de recubrimiento de liberación retardada puede ser la siguiente: El talco y el citrato de trietilo se homogeneizan en el disolvente por medio de un homogeneizador durante aproximadamente 10 minutos. La suspensión se vierte directamente en la dispersión de Eudragit® L12.5 y se agita suavemente para evitar la sedimentación. El recubrimiento se pulveriza sobre los comprimidos hasta que se aplicaron aproximadamente 5 mg/cm^2 de Eudragit® L al núcleo del comprimido.

En al menos una realización el recubrimiento de control de la liberación es una formulación de recubrimiento de liberación sostenida para el núcleo del comprimido; la

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formulación de recubrimiento que se aplica al núcleo comprende:

Eudragit RL 12.5	10 % en peso de la suspensión de recubrimiento
Eudragit RS 12.5	30 % en peso de la suspensión de recubrimiento
Sebacato de dibutilo	0,5 % en peso de la suspensión de recubrimiento
Talco	3,5 g en peso de la suspensión de recubrimiento
Estearato de magnesio	1 % en peso de la suspensión de recubrimiento
Acetona	27,5 % en peso de la suspensión de recubrimiento
Alcohol isopropílico	27,5 % en peso de la suspensión de recubrimiento

Sólidos totales = 10 %

Contenido del polímero de la suspensión = 5 %

La preparación de la formulación de recubrimiento de liberación sostenida puede ser la siguiente: Se mezclan el sebacato de dibutilo, el talco y el estearato de magnesio y se dispersan finamente junto con los diluyentes acetona y alcohol isopropílico. La suspensión se combina luego con las dispersiones de polímero Eudragit®. El recubrimiento se pulveriza sobre el núcleo hasta que se aplicaron aproximadamente 10 mg/cm^2 del polímero al núcleo.

En al menos una realización el recubrimiento de control de la liberación es un recubrimiento mezcla de polímeros que posee un polímero dependiente del pH (Eudragit® L 30D 55) en combinación con un polímero de liberación sostenida (Aquacoat®); la formulación de recubrimiento que se aplica al núcleo comprende:

Aquacoat (etilcelulosa 30 %)	21 % en peso de la suspensión de recubrimiento
Eudragit L30 D 55	21 % en peso de la suspensión de recubrimiento
Citrato de trietilo	3 % en peso de la suspensión de recubrimiento

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Agua	55 % en peso de la suspensión de recubrimiento

Sólidos totales = 15,6 %
Contenido del polímero de la suspensión = 12,6 %
La aplicación del recubrimiento mezcla de polímeros puede ser la siguiente: Recubrimiento aplicado a una tasa de aplicación de 10 mg/cm^2 de polímero al núcleo de fármaco.

En al menos una realización el recubrimiento de control de la liberación es un recubrimiento de fármaco (Citalopram) encima de un núcleo de sal de bupropion; la formulación de recubrimiento que se aplica al núcleo comprende:

Kollidon VA64	2,5 % en peso de la suspensión de recubrimiento de fármaco
(Copolímero de vinilpirrolidona-acetato de vinilo)	
Klucel ™ EF	2,5 % en peso de la suspensión de recubrimiento de fármaco
(Hidroxipropilcelulosa)	
Citalopram	2 % en peso de la suspensión de recubrimiento de fármaco
Talco	3 % en peso de la suspensión de recubrimiento de fármaco
2-propanol	90 % en peso de la suspensión de recubrimiento de fármaco

Sólidos totales = 10 %
Contenido del polímero de la suspensión = 5 %
La aplicación de la formulación de recubrimiento de fármaco puede ser la siguiente: El recubrimiento de fármaco se pulveriza sobre los comprimidos hasta que se aplica la cantidad deseada de Citalopram.

Posteriormente se puede aplicar una capa protectora como un recubrimiento cosmético y también para prevenir la adhesión del comprimido; la formulación de la capa protectora que se aplica al núcleo recubierto de fármaco comprende:

Kollidon VA64	2,5 % en peso de la suspensión de capa protectora
(Copolímero de vinilpirrolidona-acetato de vinilo)	
Klucel ™ EF	2,5 % en peso de la suspensión de capa protectora
(Hidroxipropilcelulosa)	

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Talco	2,5 % en peso de la suspensión de capa protectora
Alcohol isopropílico	92,5 % en peso de la suspensión de capa protectora

Sólidos totales = 7,5 %
Contenido del polímero de la suspensión = 5 %
La aplicación de la formulación de la capa de protección puede ser la siguiente: La capa se aplica hasta un aumento de peso de 2 % (expresado como % del núcleo de comprimido recubierto de fármaco).

El recubrimiento de control de la liberación de liberación extendida (XL)

El recubrimiento de control de la liberación XL es un recubrimiento semipermeable que comprende un polímero formador de película, insoluble en agua y permeable al agua, opcionalmente un polímero soluble en agua y opcionalmente un plastificante.

Los ejemplos no limitantes de polímeros formadores de película, insolubles en agua y permeables al agua, útiles para el recubrimiento de control de la liberación XL incluyen éteres de celulosa, ésteres de celulosa y alcohol polivinílico. Por ejemplo, los polímeros formadores de película, insolubles en agua y permeables al agua pueden ser etilcelulosas y se pueden seleccionar entre los siguientes: etilcelulosa grados PR100, PR45, PR20, PR10 y PR7 (Ethocel®, Dow), y cualquier combinación de ellos. En al menos una realización de la invención, la etilcelulosa de grado PR100 es el polímero formador de película, insoluble en agua y permeable al agua. La cantidad de polímero formador de película insoluble en agua y permeable al agua puede variar de 1 % a 12 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones la cantidad de polímero formador de película, insoluble en agua y permeable al agua está presente en una cantidad de 5 % a 10 % y en otras realizaciones de 6 % a 8 % en peso del peso seco del comprimido. En ciertas realizaciones de los comprimidos de liberación modificada de 174 mg de dosis de la invención, la cantidad de polímero formador de película insoluble en agua y permeable al agua es de 3 % a 8 % en peso del peso seco del comprimido y en otras realizaciones de 6 % a 7 % en peso del peso seco del

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comprimido. En lo que se refiere al recubrimiento de control de la liberación, la cantidad de polímero formador de película, insoluble en agua y permeable al agua en ciertas realizaciones del comprimido de 174 mg de dosis es de 35 % a 60 % en peso del peso seco del recubrimiento de control de la liberación y en otras realizaciones de 40 % a 50 % en peso del peso seco del recubrimiento de control de la liberación. En ciertas realizaciones de los comprimidos de liberación modificada de 348 mg de dosis de la invención, la cantidad de polímero formador de película, insoluble en agua y permeable al agua es de 2 % a 5 % en peso del peso seco del comprimido y en otras realizaciones de 3 % a 4 % en peso del peso seco del comprimido. En lo que se refiere al recubrimiento de control de la liberación en sí, el polímero formador de película, insoluble en agua y permeable al agua en ciertas realizaciones de los comprimidos de 348 mg de dosis está presente en una cantidad de 40 % en peso del peso seco del recubrimiento de control de la liberación.

Los ejemplos no limitantes de polímeros solubles en agua útiles para el recubrimiento de control de la liberación XL incluyen polivinilpirrolidona, hidroxipropilmetilcelulosa, hidroxipropilcelulosa y sus mezclas. En al menos una realización el polímero soluble en agua es polivinilpirrolidona (Povidona® USP). La cantidad de polímero soluble en agua puede variar de 1,5 % a 10 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones la cantidad de polímero soluble en agua es de 3 % a 8 % y en otras realizaciones de 4 % en peso del peso seco del comprimido. En lo que se refiere al recubrimiento de control de la liberación en sí, en ciertas realizaciones la cantidad de polímero soluble en agua presente es de 25 % a 55 % en peso del peso seco del recubrimiento de control de la liberación. Para ciertas realizaciones de los comprimidos de liberación extendida de 174 mg de dosis de la invención, la cantidad de polímero soluble en agua es de 3 % a 5% en peso del peso seco del comprimido y de 25 % a 50 % en peso del peso seco del recubrimiento de control de la liberación. Para ciertas realizaciones de los comprimidos de liberación extendida de la invención de 348 mg de dosis, la cantidad de polímero soluble en agua presente

es de 2 % a 5 % del peso seco del comprimido y de 40 % a 50 % en peso del peso seco del recubrimiento de control de la liberación.

En ciertas realizaciones, el recubrimiento de control de la liberación XL comprende además un plastificante. El uso de plastificantes es opcional, y se pueden agregar a las formulaciones de película de recubrimiento para modificar las propiedades físicas de un polímero para hacerlo más utilizable durante la fabricación. Los plastificantes pueden ser disolventes orgánicos de alto punto de ebullición usados para impartir flexibilidad a materiales poliméricos 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 polímero que dan lugar a diversos cambios en las propiedades del polímero incluidas una reducción de la resistencia a la tensión y un aumento de la elongación y una reducción de la temperatura de transición vítrea o la temperatura de ablandamiento del polímero. La cantidad y la elección del plastificante pueden afectar a la dureza de un comprimido e incluso pueden afectar a sus características de disolución o de desintegración, así como a su estabilidad física y química. 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 farmacéutica, ciertos plastificantes pueden actuar aumentando la hidrofilicidad de o de los recubrimientos y/o del núcleo de la forma farmacéutica en el ambiente de uso (in vitro o in vivo). Los ejemplos no limitantes de plastificantes que se pueden usar en el recubrimiento de control de la liberación descrito aquí, incluyen monoglicéridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicérido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de colza, aceite de oliva, aceite de sésamo, citrato de trietilo; alcoholes polihídricos, glicerol, glicerina, sorbitol, ésteres 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 epoxidado, trimelitato de triisoctilo, ftalato de dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, 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, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de glicerol, polioles (p. ej., polietilenglicol) de diversos pesos moleculares y sus mezclas. Está contemplado y dentro del alcance de la invención, que se puede usar una combinación de plastificantes en la presente formulación. En al menos una realización de la invención, el plastificante es polietilenglicol 4000, sebacato de dibutilo o sus mezclas. La cantidad de plastificante para el recubrimiento de control de la liberación puede variar en una cantidad entre 0,5 % y 4 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad entre 2 % y 3 % en peso del peso seco del comprimido. Para ciertas realizaciones de los comprimidos de liberación extendida de 174 mg de dosis de la invención, la cantidad de plastificante presente en el recubrimiento de control de la liberación es de 1 % a 4 % en peso del peso seco del comprimido. Para ciertas realizaciones de los comprimidos de liberación extendida de 348 mg de dosis de la invención, la cantidad de plastificante presente es de 0,5 % a 4 % en peso del peso seco del comprimido. En ciertas realizaciones de ambas formas farmacéuticas de 174 mg y 348 mg, el plastificante está presente en una cantidad entre 6 % y 30 % en peso del peso seco del recubrimiento de control de la liberación. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad de 12 % en peso del peso seco del recubrimiento de control de la liberación.

La relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua para el recubrimiento de control de la liberación XL de la invención descrito aquí, puede variar de 3:1:4 a 5:1:2. Por ejemplo, en ciertas realizaciones la relación

polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua para el recubrimiento de control de la liberación XL es 4:1:3. Para ciertas realizaciones del comprimido XL la relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua en el recubrimiento de control de la liberación XL es de 7:2:6 a 19:5:18. En al menos una realización la relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua para el recubrimiento de control de la liberación XL es 13:4:12.

La preparación y aplicación del recubrimiento de control de la liberación XL pueden ser las siguientes. El polímero formador de película insoluble en agua y permeable al agua (por ejemplo, etilcelulosa) y el plastificante (por ejemplo, polietilenglicol 4000), se disuelven en un disolvente orgánico (por ejemplo, una mezcla de alcohol etílico). En la fabricación de realizaciones que no requieren un plastificante, el polímero formador de película, insoluble en agua y permeable al agua se puede disolver en el disolvente orgánico sin el plastificante. A continuación se agrega el polímero soluble en agua (por ejemplo, polivinilpirrolidona) hasta que se logra una mezcla homogénea. Después se pulveriza la solución de recubrimiento de control de la liberación resultante sobre los núcleos de los comprimidos usando un equipo de lecho fluidizado revestidor de comprimidos o cualquier otro equipo de revestimiento adecuado conocido por los técnicos en la materia, hasta que se logra el aumento de peso deseado. Posteriormente se secan los núcleos de los comprimidos recubiertos con el recubrimiento de control de la liberación. En la fabricación de las realizaciones que tienen una barrera contra la humedad, el recubrimiento de control de la liberación se seca antes de aplicar la barrera contra la humedad.

Un ejemplo del proceso de recubrimiento para el recubrimiento de control de la liberación XL es el siguiente: La solución de recubrimiento de control de la liberación XL se prepara disolviendo el polímero insoluble en agua (por ejemplo, etilcelulosa) y el

polímero soluble en agua (por ejemplo, polivinilpirrolidona) y una mezcla de alcohol etílico mientras se mezcla y se sigue con el agregado del o de los plastificantes (por ejemplo, polietilenglicol 4000 y sebacato de dibutilo). Una vez disueltos completamente, la solución se homogeneiza para obtener una mezcla uniforme de viscosidad apropiada. Este procedimiento asegura una mezcla compleja de una película permeable al agua para controlar la liberación del fármaco activo. La composición de la solución se puede formular de modo que contenga diversos niveles del polímero insoluble en agua y del polímero soluble en agua y una mezcla del o de los plastificantes. La función de liberación se controla además mediante el espesor de la película aplicada y se mide como un aumento del peso de los sólidos en el recubrimiento requerido. Los comprimidos se recubren en una paila de recubrimiento con control de la velocidad de la paila (por ejemplo, de 8 rpm a 14 rpm y en algunos casos de 12 rpm), la velocidad de pulverización (por ejemplo, de 150 g/min a 250 g/min y en algunos casos de 200 g/min), la presión de pulverización (por ejemplo, de 15 psi y 25 psi y en algunos casos de 20 psi), el volumen de suministro (de 800 a 1.000 pies cúbicos/min y en algunos casos de 900 pies cúbicos/min) y la temperatura del aire (por ejemplo, de 50°C a 60°C y en algunos casos de 55°C), controladas mediante una temperatura del lecho y/o una temperatura de salida de 38°C a 42°C y en algunos casos de 40°C. Al finalizar el ciclo de recubrimiento, los comprimidos se secan y se descargan en envases a granel. El proceso de impresión comprende la transferencia de una imagen de impresión desde una placa de impresión cubierta con tinta negra comestible y transferida mediante un rollo o almohadilla de impresión sobre la superficie de los comprimidos. Los comprimidos impresos se transfieren a través 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 técnico con experiencia apreciará que el control de la permeabilidad puede controlar la liberación de la sal de bupropion y/o la cantidad de recubrimiento aplicada a los núcleos de los comprimidos. La permeabilidad del recubrimiento de control de la liberación XL, se puede

alterar variando la relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua y/o la cantidad de recubrimiento aplicada al núcleo del comprimido. Se puede obtener una liberación más extendida con una cantidad mayor de polímero formador de película insoluble en agua y permeable al agua. La adición de otros excipientes al núcleo del comprimido también puede alterar la permeabilidad del recubrimiento de control de la liberación. Por ejemplo, si se desea que el núcleo del comprimido contenga además un agente de expansión, se puede aumentar la cantidad de plastificante en el recubrimiento de control de la liberación para hacer el recubrimiento más flexible, puesto que la presión ejercida por el agente de expansión en un recubrimiento menos flexible podría romper el recubrimiento. Además, la proporción de polímero formador de película, insoluble en agua y permeable al agua y de polímero soluble en agua, también se puede alterar dependiendo de si se desea una disolución y/o un perfil de liberación más rápidos o más lentos.

Dependiendo de la disolución o del perfil de liberación in vivo deseados, el aumento del peso después de recubrir el núcleo del comprimido con el recubrimiento de control de la liberación XL variará típicamente de 3 % a 30 % del peso del núcleo del comprimido seco. Para un comprimido de liberación extendida de 174 mg de dosis de acuerdo con la presente invención, el aumento de peso puede varíar típicamente de 10 % a 17 % del peso del núcleo del comprimido seco. Por ejemplo en ciertas realizaciones, el aumento de peso es de 14 % del peso del núcleo del comprimido seco. Para los comprimidos de liberación extendida de 348 mg de dosis de la invención, el aumento de peso puede variar de 7 % a 10 % del peso del núcleo del comprimido seco. Por ejemplo en ciertas realizaciones, el aumento de peso es de 9 % del peso del núcleo del comprimido seco.

Recubrimiento de control de la liberación AQ

El recubrimiento de control de la liberación AQ es un recubrimiento de liberación controlada monolítico estable que comprende una dispersión acuosa de un copolímero de un éster neutro sin ningún grupo funcional, un poliglicol

con un punto de fusión mayor de 55°C y uno o más excipientes farmacéuticamente aceptables; donde dicha composición de recubrimiento se aplica sobre la forma farmacéutica y se cura a una temperatura al menos igual o mayor que el punto de fusión del poliglicol. La formulación de recubrimiento es muy versátil porque se puede usar para recubrir una diversidad de núcleos de fármaco y se puede manipular fácilmente para obtener el perfil de liberación del fármaco deseado.

En ciertas otras realizaciones, el recubrimiento de control de la liberación AQ comprende una dispersión acuosa de una etilcelulosa, un poliglicol con un punto de fusión mayor de 55 °C y uno o más excipientes farmacéuticamente aceptables; donde dicha composición de recubrimiento se aplica sobre la forma farmacéutica y se cura a una temperatura al menos igual o mayor que el punto de fusión del poliglicol. Ejemplos no limitantes de dispersiones acuosas de una etilcelulosa incluyen Surelease® (Colorcon, Inc., West Point, Pa., EE.UU.), y Aquacoat® (FMC Corp., Filadelfia, Pa., EE.UU.).

Los ejemplos no limitantes de copolímeros de ésteres neutros sin ningún grupo funcional que se pueden usar en el recubrimiento de control de la liberación AQ incluyen Eudragit® NE30D, Eudragit® NE40D (Röhm America LLC) y sus mezclas. En al menos una realización el polímero es Eudragit NE30D, que puede estar presente en una cantidad entre 1 % y 35 % en peso del recubrimiento de control de la liberación, dependiendo del perfil de liberación controlada deseado. También se pueden incluir agentes hidrófilos en el recubrimiento de control de la liberación AQ para promover la humectación del recubrimiento cuando está en contacto con los líquidos gastrointestinales. Los ejemplos no limitantes de dichos agentes hidrófilos incluyen polímeros hidrófilos solubles en agua como hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC) y sus combinaciones. En al menos una realización, la HPMC es el polímero hidrófilo soluble en agua. Si se van a incluir agentes hidrófilos en la composición del recubrimiento, dichos agentes pueden estar presentes en una cantidad de 0,1 % a 10 % en peso de la composición del recubrimiento. Por ejemplo, en ciertas realizaciones los agentes hidrófilos están

presentes en una cantidad entre 0,1 % y 5 %, y en otras realizaciones entre 0,1 % y 3 % en peso de la composición del recubrimiento de control de la liberación.

La formulación del recubrimiento de control de la liberación AQ también comprende un poliglicol con un punto de fusión mayor de 55°C. Los ejemplos no limitantes del poliglicol incluyen polietilenglicol 6000, polietilenglicol 8000, polietilenglicol 10000, polietilenglicol 20000 y sus mezclas. En al menos una realización, el poliglicol es el polietilenglicol 8000. El poliglicol puede estar presente en una cantidad entre 0,1 % y 5 % en peso del recubrimiento. Otros ejemplos de derivados adecuados de poliglicol con un punto de fusión de al menos 55 °C incluyen, pero no exclusivamente, Poloxamer 188, Poloxamer 338, Poloxamer 407, óxidos de polietileno, éteres alquílicos de polioxietileno y estearatos de polioxietileno.

Además de los copolímeros y el poliglicol, el recubrimiento de control de la liberación AQ comprende al menos un excipiente farmacéuticamente aceptable. Los excipientes pueden incluir pero no exclusivamente antiadherentes, emulsionantes, antiespumantes, saborizantes, colorantes, etc. Los técnicos con experiencia en el tema saben que dependiendo de la función principal a que están destinados 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 multifuncionales. Un trabajador capacitado sabrá, basado en su conocimiento técnico, qué excipientes farmacéuticamente aceptables son adecuados para la composición del recubrimiento de control de la liberación AQ deseado.

La adherencia de las películas poliméricas es un factor para el recubrimiento de las formas farmacéuticas sólidas y para el paso de curado posterior (tratamiento térmico posterior al recubrimiento). Durante el recubrimiento con polímeros celulósicos o acrílicos, puede ocurrir a veces una aglomeración no deseada y otras veces una aglomeración irreversible de varios gránulos o perlas o, en el peor de los casos, de todo el lote, especialmente a

mayores temperaturas de procesamiento del producto. En consecuencia, puede ser aconsejable la adición de antiadherente a las formulaciones de recubrimiento. Los antiadherentes que se pueden usar incluyen pero no exclusivamente ácido adípico, estearato de magnesio, estearato de calcio, estearato de cinc, aceites vegetales hidrogenados, esterotex, monoestearato de glicerilo, talco, benzoato de sodio, lauril sulfato de sodio, lauril sulfato de magnesio y sus mezclas. En al menos una realización, el antiadherente es talco. El talco también puede actuar como humectante. Las mezclas de antiadherentes son factibles. La cantidad de antiadherente en la composición del recubrimiento de control de la liberación puede estar en el rango de 1 % a 15 % en peso de la dispersión de recubrimiento de control de la liberación. Por ejemplo, en ciertas realizaciones el antiadherente está presente en una cantidad entre 1 % y 7 % en peso de la dispersión de recubrimiento de control de la liberación.

Los antiespumantes, que se pueden incluir en la composición del recubrimiento de control de la liberación AQ incluyen aceite de silicona, simeticona y sus mezclas. En al menos una realización, el antiespumante es simeticona. El antiespumante puede estar presente en una cantidad de hasta 0,5 % en peso de la composición del recubrimiento de control de la liberación AQ. Por ejemplo, en cierta realización el antiespumante está presente en una cantidad entre 0,1 % y 0,4% en peso de la composición del recubrimiento de control de la liberación AQ.

El o los emulsionantes (también denominados emulsificantes o emulgentes) se pueden incluir para facilitar la emulsificación durante la fabricación del recubrimiento de control de la liberación AQ y también para proporcionar estabilidad a la emulsión durante el período máximo de almacenamiento del producto. Los ejemplos no limitantes de emulsionantes incluyen materiales de origen natural y sus derivados semisintéticos, como los polisacáridos, así como los ésteres de glicerol, los éteres de celulosa, los ésteres de sorbitán y los polisorbatos. Las mezclas son factibles. En al menos una realización el emulsionante es

Polisorbato 80 (monooleato de polioxietilensorbitán) (Tween ™ 80). El o los emulsionantes pueden estar presentes en una cantidad de hasta 0,5 % en peso de la composición del recubrimiento de control de la liberación AQ. Por ejemplo, en ciertas realizaciones el o los emulsionantes están presentes en una cantidad entre 0,1 % y 0,3 % en peso de la composición del recubrimiento de control de la liberación AQ.

Los colorantes de la fórmula de la película de recubrimiento pueden ser colorantes insolubles en agua (pigmentos). Los pigmentos tienen ciertas ventajas sobre los colorantes solubles en agua en que tienden a ser químicamente más estables frente a la luz, proporcionan mejor opacidad y poder de cobertura y optimizan la impermeabilidad de una película dada al vapor de agua. Los ejemplos no limitantes de colorantes adecuados incluyen pigmentos de óxido de hierro, dióxido de titanio y lacas de aluminio. Las mezclas son factibles. En al menos una realización el pigmento es dióxido de titanio. El pigmento o colorante puede estar presente en una cantidad entre 0,1 % y 10 % en peso de la composición del recubrimiento de control de la liberación AQ. Por ejemplo, en ciertas realizaciones el pigmento o colorante está presente en una cantidad entre 0,1 % y 5 %, y en otras realizaciones entre 0,1 % y 2 % en peso de la composición del recubrimiento de control de la liberación AQ.

El recubrimiento de control de la liberación AQ se puede aplicar sobre un núcleo que comprende una cantidad eficaz de la sal de bupropion mediante un proceso, que implica la pulverización de la solución o suspensión de recubrimiento sobre un lecho de núcleos de los comprimidos. Algunos ejemplos de equipo adecuado para el recubrimiento con película incluyen: Accela Cota (Manesty Machines, Liverpool, Reino Unido), Hi-Coater (Freund Company, Japón), Driacoater (Driam Metallprodukt GmbH, Alemania), HTF/150 (GS, Italia) e IDA (Dumoulin, Francia). Los ejemplos de unidades que funcionan sobre el principio de lecho fluidizado incluyen: Aeromatic (Fielder, Suiza y Reino Unido) y Glatt AG (Suiza). En al

menos una realización, el aparato usado para el recubrimiento con película es el Accela Cota.

El líquido de recubrimiento se puede suministrar al aparato de recubrimiento desde una bomba peristáltica a la velocidad deseada y pulverizar sobre los núcleos de los comprimidos rotando o fluyendo. Los núcleos de los comprimidos se precalientan a 30°C. Durante el proceso de recubrimiento, el intervalo de temperatura del producto se mantiene entre 25°C y 35°C ajustando la velocidad de flujo de entrada y salida del aire, la temperatura de entrada del aire y la velocidad de pulverización. Se aplica una única capa de recubrimiento y una vez que se completa la pulverización, los núcleos de los comprimidos recubiertos se secan entre 30°C y 40°C durante 3 a 5 minutos a una velocidad de la paila baja y un flujo de aire bajo. La paila se reajusta para hacer avanzar la velocidad y el secado continuos durante 12 a 15 minutos.

Los núcleos de los comprimidos recubiertos se colocan sobre una bandeja y se curan (tratamiento térmico post recubrimiento) en una estufa eléctrica u horno de vapor a una temperatura por encima de la temperatura del punto de fusión del polietilenglicol o uno de sus derivados. La temperatura de curado es preferentemente superior al punto de fusión del polietilenglicol o de su derivado. El tiempo de curado es preferentemente de 2 a 7 horas. Los comprimidos recubiertos curados se enfrían posteriormente a temperatura ambiente.

El recubrimiento de control de la liberación AQ es muy versátil. La duración y el tiempo del retraso se pueden controlar mediante la velocidad de hidratación y el espesor del recubrimiento. La velocidad de liberación del fármaco posterior al retraso se puede determinar mediante el espesor y la permeabilidad del recubrimiento hidratado. Por lo tanto, es posible regular la velocidad de hidratación y permeabilidad del recubrimiento de control de la liberación AQ para que se pueda lograr el perfil deseado de liberación controlada del fármaco. No se prefiere ningún espesor en particular para el recubrimiento, ya que éste dependerá del perfil de liberación controlada deseado. Otros parámetros en combinación con el espesor del recubrimiento incluyen

variar las concentraciones de algunos de los ingredientes de la composición del recubrimiento estable de la invención descrita y/o variar la temperatura de curado y la duración del curado de los núcleos de los comprimidos recubiertos. El técnico con experiencia sabrá qué parámetros o combinación de parámetros cambiar para un perfil de liberación controlada deseado.

El recubrimiento de barrera contra la humedad

En ciertas realizaciones, se aplica una barrera contra la humedad opcional directamente sobre el recubrimiento de control de la liberación. En otras realizaciones no se incluye una barrera contra la humedad en la forma farmacéutica. La barrera contra la humedad comprende típicamente un polímero entérico (por ejemplo, polímero acrílico), un potenciador de la penetración y opcionalmente un plastificante.

En ciertas realizaciones, el polímero entérico es un polímero acrílico. Por ejemplo, el polímero acrílico puede ser un copolímero del ácido metacrílico tipo C de [poli(ácido metacrílico, metacrilato de metilo) 1:1] que se comercializa con el nombre comercial Eudragit® (por ejemplo, Eudragit L 30 D-55). El copolímero del ácido metacrílico puede estar presente en una cantidad, que puede variar de 1 % a 3 % del peso seco del comprimido y de 55 % a 70 % del peso seco de la barrera contra la humedad. Para los comprimidos de liberación extendida de 174 mg de dosis de la presente invención, el copolímero del ácido metacrílico puede variar de 2 % a 3 % del peso seco del comprimido. Por ejemplo en ciertas realizaciones, la cantidad de copolímero del ácido metacrílico está presente en 2,5 % del peso seco del comprimido. En lo que se refiere a la barrera contra la humedad en sí, la cantidad de copolímero del ácido metacrílico puede estar presente en una cantidad entre 55 % y 70 % en peso del peso seco de la barrera contra la humedad. Por ejemplo, en ciertas realizaciones el copolímero del ácido metacrílico está presente en una cantidad de 60 % del peso seco de la barrera contra la humedad. Para los comprimidos de liberación extendida de 348 mg de dosis de la presente invención, la cantidad de copolímero del ácido metacrílico puede variar de 1,5 % a 3 % del peso seco del comprimido. Por ejemplo, en ciertas

realizaciones, la cantidad de copolímero del ácido metacrílico está presente en 2 % en peso del peso seco del comprimido. En lo que se refiere al recubrimiento en sí, el copolímero del ácido metacrílico estará presente típicamente en una cantidad entre 55 % y 70 % del peso seco de la barrera contra la humedad. Por ejemplo, en ciertas realizaciones el copolímero del ácido metacrílico está presente en una cantidad de 60 % del peso seco de la barrera contra la humedad.

Se sabe en el área que los copolímeros del ácido metacrílico se pueden tornar quebradizos y que los recubrimientos que contienen copolímeros del ácido metacrílico se podrían hacer más elásticos y flexibles mediante adición de un plastificante. En ciertas realizaciones la barrera contra la humedad contiene un plastificante. Los ejemplos no limitantes de plastificantes útiles para el recubrimiento de barrera contra la humedad descrito aquí incluyen monoglicéridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicérido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de colza, aceite de oliva, aceite de sésamo, citrato de trietilo; alcoholes polihídricos, glicerol, glicerina, sorbitol, ésteres 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 epoxidado, trimelitato de triisoctilo, ftalato de dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, 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, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de glicerol y sus mezclas, polioles (p. ej., polietilenglicol) de diversos pesos moleculares y sus mezclas. En ciertas realizaciones, el plastificante en el recubrimiento de

barrera contra la humedad comprende una combinación de citrato de trietilo y polietilenglicol 4000 (por ejemplo, Carbowax® 4000). En algunas de estas realizaciones, la relación entre citrato de trietilo y polietilenglicol 4000 es 1:2. El plastificante puede estar presente en una cantidad que puede variar de 0,2 % a 0,5 %. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad entre 0,2 % y 0,4 % del peso seco del comprimido. El plastificante puede estar presente en una cantidad de 0,35 % del peso seco del comprimido para un comprimido de 174 mg; y en una cantidad entre 0,2 % y 0,4 % del peso seco del comprimido para un comprimido de 348 mg. En lo que se refiere a la barrera contra la humedad en sí, el plastificante si está presente puede estar presente típicamente en una cantidad entre 1 % y 30 % en peso del peso seco de la barrera contra la humedad. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad entre 10 % y 14 % del peso seco de la barrera contra la humedad para ambos comprimidos de liberación extendida de 174 mg y de 348 mg de dosis de la presente invención. Es bien conocido por los técnicos en la materia que dependiendo de la función principal a la que están destinados, los excipientes que se van a usar en los comprimidos se subclasifican en diferentes grupos. Sin embargo, un excipiente puede afectar a las propiedades de un fármaco o del comprimido en su totalidad de una serie de maneras y por consiguiente muchas sustancias usadas en las formulaciones de comprimidos pueden describirse como multifuncionales. Por lo tanto, el polietilenglicol usado en la combinación plastificante para la barrera contra la humedad puede servir no sólo para aumentar la hidrofilicidad de la barrera contra la humedad, sino que también puede actuar como un deslizante.

La barrera contra la humedad puede además comprender un potenciador de la penetración que puede aumentar su hidrofilicidad y también puede actuar como un deslizante. El potenciador de la penetración puede ser una sustancia hidrófila y se puede seleccionar entre las siguientes: polímeros hidrófilos como hidroxipropilmetilcelulosa, éteres de celulosa y materiales derivados proteicos de estos polímeros, los éteres de celulosa, especialmente se prefieren hidroxialquilcelulosas y

carboxialquilcelulosas. Además, se pueden usar polímeros solubles en agua sintéticos, como polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de polietileno, etc., polidextrosa soluble en agua, sacáridos y polisacáridos, como pullulan, dextrano, sacarosa, glucosa, lactosa, fructosa, manitol, manosa, galactosa, sorbitol y similares. En al menos una realización de la presente invención, el polímero hidrófilo comprende hidroxipropilmetilcelulosa. Otros ejemplos no limitantes de los potenciadores de la penetración incluyen sales de metales alcalinos como óxido de aluminio, 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 similares. Los sólidos formadores de poros también pueden ser polímeros que son solubles en el ambiente de uso, como los Carbowax®, Carbopol® y similares. Los formadores de poros abarcan dioles, polioles, alcoholes polihídricos, polialquilenglicoles, poliglicoles, poli(a-w)alquilendioles y similares. Otros potenciadores de la penetración que pueden ser útiles en las formulaciones de la presente invención incluyen almidón, almidón modificado y derivados del almidón, gomas, incluidas, pero no exclusivamente, goma xantano, ácido algínico, otros alginatos, bentonita, veegum (silicato de aluminio y magnesio), agar, goma guar, goma de algarrobo, goma arábiga, quince psyllium, semilla de lino, goma de quimbombó, arabinogalactano, pectina, goma tragacanto, escleroglucano, dextrano, amilosa, amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de intercambio iónico, como polimetacrilato de potasio, carragenina, carragenina kappa, carragenina lambda, goma karaya, goma biosintética, etc. Otros formadores de poros incluyen materiales útiles para hacer láminas porosas en los ambientes de uso, como policarbonatos compuestos de poliésteres del ácido carbónico lineales en los que los grupos carbonato reaparecen en la cadena polimérica, materiales microporosos como bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas, copolímeros modacrílicos microporosos, estireno-acrílico microporoso y sus copolímeros, polísulfonas porosas, poli(vinilideno) halogenado, policloroéteres, polímeros de acetal, poliésteres preparados por esterificación de un ácido dicarboxílico o anhídrido con un alquilenpoliol,

poli(sulfuros de alquileno), fenólicos, poliésteres, polímeros porosos asimétricos, polímeros olefínicos reticulados, homopolímeros hidrófilos microporosos, copolímeros o interpolímeros con una menor densidad aparente y otros materiales similares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas), poli(benzimidazoles), colodión, proteínas regeneradas, poli(vinilpirrolidona) reticulada semisólida, dióxido de silicio, sílice coloidal, celulosa microcristalina y cualquier combinación de éstos. En al menos una realización de la invención el potenciador de la penetración es dióxido de silicio (por ejemplo, Syloid® 244FP). La cantidad de potenciador de la penetración puede variar de 0,5 % a 1 % en peso del peso seco del comprimido y de 25 % a 30 % en peso del peso seco de la barrera contra la humedad. Para los comprimidos de liberación extendida de 174 mg de dosis de la invención, el potenciador de la penetración puede estar presente en una cantidad de 0,5 % a 2 % del peso seco del comprimido y de 20 % a 40 % en peso del peso seco de la barrera contra la humedad. Por ejemplo, en ciertas realizaciones del comprimido de 174 mg de dosis, el potenciador de la penetración está presente en una cantidad entre 25 % y 30 % en peso del peso seco de la barrera contra la humedad. Para los comprimidos de liberación extendida de 348 mg de dosis de la invención, el potenciador de la penetración puede estar presente en una cantidad que puede variar de 0,5 % a 2 % en peso del peso seco del comprimido y de 20 % a 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 está presente en una cantidad entre 25 % y 30 % en peso del peso seco de la barrera contra la humedad.

En al menos una realización de la invención, la relación copolímero del ácido metacrílico:plastificante:potenciador de la penetración es 13:2:5.

La preparación 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. Después el copolímero del ácido metacrílico (por ejemplo, Eudragit® L 30 D-55), se tamiza y se agrega a la mezcla plastificante y se mezcla hasta homogeneizar. En un recipiente separado se disuelve el potenciador de la penetración (por ejemplo, dióxido de silicio) en agua hasta que se logra una mezcla homogénea. Después se combinan el plastificante y la mezcla de copolímero del ácido metacrílico 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 núcleos de los comprimidos recubiertos con el recubrimiento de control de la liberación usando un aparato de lecho fluidizado revestidor de comprimidos u otro aparato de recubrimiento adecuado conocido en el área hasta que se logra el aumento de peso deseado. Los comprimidos recubiertos con la barrera contra la humedad se secan posteriormente antes de envasar.

La barrera contra la humedad se aplica a los núcleos de los comprimidos con recubrimiento de control de la liberación de tal manera que el aumento de peso sea no más de 6 % del peso seco del comprimido tanto para los comprimidos de liberación extendida de 174 mg como de 348 mg de la presente invención. En al menos una realización el aumento de peso es no más de 3,5 % del peso seco del comprimido tanto para los comprimidos de liberación extendida de 174 mg como de 348 mg de acuerdo con la presente invención. La cantidad de barrera contra la humedad aplicada en general no torna al comprimido de liberación extendida descrito aquí significativamente más resistente al líquido gástrico. Sin embargo, la barrera contra la humedad puede tener repercusión sobre las características de liberación del fármaco.

La barrera contra la humedad como se usa aquí si está presente en el medicamento de bromhidrato de bupropion no actúa habitualmente como un recubrimiento entérico. Aunque en el área se hace referencia y se usa el copolímero del ácido metacrílico, Eudragit® L 30 D-55, en formulaciones de recubrimiento entérico, su funcionalidad depende de la formulación y de la cantidad de material aplicado. Como se sabe en el área, un recubrimiento entérico se aplica cuando un fármaco puede

ser destruido o inactivado por los jugos gástricos o cuando el fármaco puede irritar la mucosa gástrica. Para cumplir con los requisitos de un recubrimiento entérico, la prueba según se describe en la USP (método A o B) estipula que después de 2 horas en medio ácido (HCl 0,1 N), ningún valor individual de al menos seis experimentos excede de 10 % del fármaco activo disuelto y no menos de 75 % se disuelve a los 45 minutos a pH 6,8. La barrera contra la humedad en general no cumple con este requisito por las razones siguientes aunque la sal de bupropion (por ejemplo, bromhidrato de bupropion) no es afectada negativamente en los medios ácidos ni es irritante para la mucosa gástrica: (1) para obtener integridad entérica con una película que contiene Eudragit® L 30 D-55, se recomienda un aumento de peso de 6 % a 8% basado en el polímero seco por unidad de dosificación. La cantidad de sólidos de Eudragit® L 30 D-55 aplicada sobre los núcleos de los comprimidos con recubrimiento de control de la liberación no es más de 6 % y en al menos una realización, no es más de 3 %, (2) si fuera necesaria la integridad entérica, la prueba de disolución para el producto terminado (es decir, los núcleos de los comprimidos recubiertos con barrera contra la humedad) en el tiempo de muestreo a las 2 horas no estipularía un límite de no más de 20 %, y (3) las pruebas analíticas realizadas sobre estos recubrimientos indican que los recubrimientos no cumplen con todos los requisitos de la prueba como un producto con recubrimiento entérico según se define por los métodos de prueba de la USP.

El comprimido XL de la invención proporciona una liberación extendida de la sal de bupropion. En general no hay presente ningún agente formador de poros en la formulación de recubrimiento XL. Se proporciona una formulación de bromhidrato de bupropion de liberación extendida tal que después de 2 horas, se libera no más de 20 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones, se libera de 2 % a 18 %, de 4 % a 8 % o 5 % del contenido de bromhidrato de bupropion después de 2 horas. Después de 4 horas, se libera de 15 % a 45 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera de 21 % a 37 %, de 28 % a 34 % o 32 % del contenido de bromhidrato de bupropion después de 4 horas.

Después de 8 horas, se libera de 40 % a 90 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera de 60 % a 85 %, de 68 % a 74 % o 74 % del contenido de bromhidrato de bupropion después de 8 horas. Después de 16 horas se libera no menos de 80 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera no menos de 93 %, no menos de 96 %, o no menos de 99 % del contenido de bromhidrato de bupropion.

Además, se proporcionan comprimidos de liberación extendida en los que después de 2 horas se libera no más de 40 % (por ejemplo, 33 %) del bromhidrato de bupropion; después de 4 horas se libera de 40 % a 75% del bromhidrato de bupropion (por ejemplo, 59 %); después de 8 horas se libera al menos 75 % del bromhidrato de bupropion (por ejemplo, 91 %); y después de 16 horas se libera al menos 85 % del bromhidrato de bupropion (por ejemplo, 97 %). En todos los casos cuando aquí se proporcionan perfiles de disolución reales o proféticos esto significa que el medicamento posee dicho perfil en al menos un medio de disolución en las condiciones prescritas como las identificadas aquí y que son bien conocidas por los técnicos con experiencia en el tema. Dichos medios de disolución, condiciones de disolución y aparato para realizarla se especifican en la farmacopea de los Estados Unidos (USP) y sus contrapartes europea y japonesa. Además, se proporcionan ejemplos específicos en esta solicitud.

Comprimidos de absorción mejorada (EA)

En otro aspecto de la presente invención, se proporciona un comprimido de absorción mejorada (EA) que tiene un núcleo que comprende una sal farmacéuticamente aceptable de bupropion y excipientes convencionales, donde la sal de bupropion es más estable que el clorhidrato de bupropion como el bromhidrato de bupropion. El núcleo está rodeado por un recubrimiento EA, que controla la liberación de la sal de bupropion. En ciertas realizaciones, el recubrimiento EA consta de una capa. Una ventaja del comprimido EA incluye la reducción de la cantidad de fármaco requerida en la composición, que a su vez puede dar lugar a una reducción de los efectos

colaterales. El comprimido EA de la invención tiene una inesperada estabilidad mejorada.

El núcleo EA

El núcleo del comprimido EA comprende una cantidad eficaz de una sal de bupropion, un aglutinante y un lubricante y puede contener otros excipientes inertes convencionales. La cantidad de sal de bupropion presente en el núcleo EA puede variar de 40 % a 99 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones el bromhidrato de bupropion está presente en una cantidad entre 50 % y 95 %, y en otras realizaciones en una cantidad entre 70 % y 90 % en peso del peso seco del comprimido. El comprimido comprende una cantidad eficaz de sal de bupropion que puede variar de 50 mg a 450 mg. Por ejemplo, el comprimido EA puede comprender 150 mg o 300 mg de bromhidrato de bupropion. Para un comprimido de 150 mg de dosis el bromhidrato de bupropion puede estar presente en una cantidad entre 76 % y 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 80 % y 83 % en peso del peso seco del comprimido. Para ambos comprimidos EA de bromhidrato de bupropion tanto de 150 mg como de 300 mg de dosis de la invención, el bromhidrato de bupropion puede estar presente en 94 % en peso del núcleo seco para cada dosis.

Se puede agregar un aglutinante (también denominado a veces adhesivo) a una mezcla de relleno y fármaco para aumentar la fuerza mecánica de los gránulos y los comprimidos durante la formación. Los aglutinantes se pueden agregar a la formulación de diferentes maneras: (1) como un polvo seco, que se mezcla con otros ingredientes antes de la aglomeración húmeda, (2) como una solución, que se usa como líquido de aglomeración durante la aglomeración húmeda, y se denomina solución aglutinante, y (3) como un polvo seco, que se mezcla con los otros ingredientes antes de la compactación, (denominado aglutinante seco). Las soluciones aglutinantes son una manera común de incorporar un aglutinante a los gránulos. En ciertas realizaciones, el aglutinante usado en los comprimidos EA está en forma de una solución aglutinante. Los ejemplos no limitantes de aglutinantes incluyen aceite vegetal hidrogenado, aceite

de ricino, parafina, alcoholes alifáticos superiores, ácidos alifáticos superiores, ácidos grasos de cadena larga, ésteres de ácidos grasos, materiales similares a cera como los alcoholes grasos, ésteres de ácidos grasos, glicéridos de ácidos grasos, grasas hidrogenadas, hidrocarburos, ceras normales, ácido esteárico, alcohol estearílico, polímeros hidrófobos e hidrófilos que tiene esqueletos hidrocarbonados y sus mezclas. Ejemplos específicos de polímeros solubles en agua aglutinantes incluyen almidón modificado, gelatina, polivinilpirrolidona, derivados de celulosa (como por ejemplo hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa (HPC)), alcohol polivinílico y sus mezclas. La cantidad de aglutinante presente puede variar de 0,5 % a 25 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones de la invención, la cantidad de aglutinante presente varía de 0,5 % a 15 % en peso del peso seco del comprimido; en otras realizaciones de 1 % a 6 % en peso del peso seco del comprimido; y aún en otras realizaciones es de 3 % en peso del peso seco del comprimido. Para ambos comprimidos EA de 150 mg y de 300 mg de dosis, el aglutinante puede estar presente en una cantidad entre 1 % y 6 % en peso del peso de cada núcleo seco. Por ejemplo, en ciertas realizaciones el aglutinante está presente en una cantidad de 3 % en peso del peso de cada núcleo seco. En al menos una realización de la invención el aglutinante es el alcohol polivinílico.

Se pueden agregar lubricantes a las formulaciones farmacéuticas para reducir cualquier fricción que ocurra entre el sólido y la pared de la matriz durante la fabricación de comprimidos. Una fricción elevada durante la compresión puede causar una serie de problemas, entre otros una inadecuada calidad del comprimido (decapado o incluso fragmentación de comprimidos durante la expulsión y rayones verticales en los bordes del comprimido) y puede incluso detener la producción. En consecuencia, se pueden agregar lubricantes a ciertas formulaciones de comprimidos de la presente invención incluida la formulación de comprimidos EA descrita aquí. Los ejemplos no limitantes de lubricantes útiles para el núcleo EA incluyen behenato de glicerilo, ácido esteárico, aceites vegetales hidrogenados (como aceite de semilla de algodón

hidrogenado (Sterotex®), aceite de soja hidrogenado (Sterotex® HM) y aceite de soja hidrogenado y cera de ricino (Sterotex® K), alcohol estearílico, leucina, polietilenglicol (PM 1.450, adecuadamente 4.000 y mayor), estearato de magnesio, monoestearato de glicerilo, ácido esteárico, polietilenglicol, polímeros de óxido de etileno (por ejemplo, los disponibles bajo la marca registrada Carbowax® de Union Carbide, Inc., Danbury, Conn.), lauril sulfato de sodio, lauril sulfato de magnesio, oleato de sodio, estearil fumarato de sodio, DL-leucina, sílice coloidal y otros conocidos en el área. En al menos una realización de la invención, el lubricante es behenato de glicerilo (por ejemplo, Compritol® 888). La cantidad de lubricante presente puede variar de 0,1 % a 6 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones la cantidad de lubricante presente es de 3 % en peso del peso seco del comprimido. Para ciertas realizaciones de los comprimidos EA de 174 mg y 348 mg de dosis de la invención, el lubricante está presente en una cantidad de 3 % en peso del peso seco del comprimido y de 1 % a 6 % en peso del peso del núcleo seco. Por ejemplo, en ciertas realizaciones el lubricante está presente en una cantidad de 3 % en peso del peso del núcleo seco tanto para los comprimidos EA de 174 mg como los de 348 mg de dosis.

En esta etapa, la formulación del núcleo EA es una formulación de liberación inmediata sin recubrir que da lugar a 100 % de disolución de la sal de bupropion en 1 hora. En al menos una realización el núcleo EA es una formulación de matriz de liberación normal. En ciertas realizaciones el núcleo comprende una cantidad eficaz de bromhidrato de bupropion, un aglutinante (por ejemplo, alcohol polivinílico) y un lubricante (por ejemplo, behenato de glicerilo). Sin embargo, si fuera necesario, se pueden agregar otros excipientes inertes compatibles con los objetivos de la invención a la formulación del núcleo. Se pueden agregar otros excipientes inertes para facilitar la preparación y/o mejorar la aceptabilidad por el paciente de la forma farmacéutica final EA de sal de bupropion como la descrita aquí. Los excipientes inertes adicionales son bien conocidos por los técnicos con experiencia y se pueden encontrar en la bibliografía pertinente, por ejemplo en el Handbook of Pharmaceutical

Excipients. Ejemplos no limitantes de tales excipientes incluyen lactosa secada por aspersión, sorbitol, manitol y cualquier derivado de celulosa.

En ciertas realizaciones, los gránulos que se van a comprimir para formar el núcleo del comprimido EA de la invención descrito aquí se preparan mediante el proceso de granulación húmeda. La granulación húmeda implica la agitación de un polvo (el fármaco activo) por convención en presencia de un líquido (la solución aglutinante) seguida de secado. Para formar los gránulos, que finalmente se van a comprimir para obtener los núcleos de los comprimidos, primero se granula la sal de bupropion, por ejemplo con una solución aglutinante, en un granulador, por ejemplo un granulador de lecho fluidizado como un granulador de lecho fluidizado fabricado por Glatt (Alemania) o Aeromatic (Suiza). El aglutinante (por ejemplo, alcohol polivinílico) se disuelve o se dispersa primero en un disolvente adecuado (por ejemplo, agua). Luego se pulveriza en la parte superior la solución aglutinante sobre el fármaco en un granulador (p. ej., un granulador de lecho fluidizado). Alternativamente, la granulación también se puede llevar a cabo en un mezclador convencional o de alto cizallamiento. Si fuera necesario, los excipientes inertes adicionales (por ejemplo, un relleno) se pueden mezclar con la sal de bupropion antes del paso de granulación.

Posteriormente se secan los gránulos formados y luego se tamizan antes de mezclar dichos gránulos con el lubricante. En ciertas realizaciones los gránulos secos se tamizan a través de un tamiz de 1,4 mm de malla. Los gránulos tamizados se mezclan luego con el lubricante, y si fuera necesario, con cualquier otro excipiente inerte adicional, que pueda mejorar el procesamiento de los comprimidos EA de la invención. La mezcla de los gránulos con el lubricante y si fuera necesario, con cualquier otro excipiente inerte, como por ejemplo un deslizante, se puede llevar a cabo en un mezclador en V u otro aparato de mezcla adecuado. Los deslizantes pueden mejorar la capacidad de fluir del polvo. Esto es especialmente importante durante la producción de comprimidos a velocidades altas de producción y durante la compactación directa. Sin embargo, debido a que el

flujo adecuado requerido es un flujo alto, a menudo también se agrega un deslizante a la granulación antes de la formación de comprimidos. Posteriormente los gránulos mezclados se comprimen en forma de comprimidos y de aquí en adelante se denominan núcleos de los comprimidos. Los núcleos de los comprimidos se pueden obtener mediante el uso de técnicas y equipo corrientes bien conocidos por los técnicos con experiencia. En ciertas realizaciones los núcleos de los comprimidos se obtienen mediante una compresora rotatoria (también denominada compresora multiestación) equipada con punzones adecuados.

Los gránulos también se pueden preparar usando otros procesos conocidos por los técnicos con experiencia. Los ejemplos de otros procesos de fabricación de gránulos incluyen granulación seca (por ejemplo, aglutinación, compactación con rodillos), compresión directa, extrusión, esferonización, granulación por fusión y granulación rotatoria.

Un ejemplo del proceso de granulación para los núcleos EA (lote de 60 kg) es el siguiente: Se usa un procesador de lecho fluidizado para la granulación a fin de aglomerar las partículas de los materiales para obtener un tamaño de partícula uniforme para la mezcla final. La solución de granulación se prepara por disolución del aglutinante (p. ej., alcohol polivinílico) en agua purificada caliente mientras se mezcla. Se puede ajustar el contenido porcentual de sólidos para obtener una viscosidad que permita controlar la acumulación (tamaño de aglomeración) del material. Una viscosidad menor conduce a partículas más pequeñas y una viscosidad mayor conduce a partículas más grandes. Además la velocidad de aplicación (p. ej. de 150 g/min a 250 g/min; o 200 g/min), la posición de la pistola de pulverización (p. ej. en la posición central) y el tamaño de la boquilla (p. ej. de 0,5 mm a 2 mm; o 1 mm) y la presión de pulverización (p. ej. de 20 psi a 40 psi; o 30 psi) contribuyen a controlar el tamaño de partícula. El material activo se fluidiza y se calienta (p. ej., de 35°C a 45 °C; o 40 °C) antes de comenzar a aplicar la solución. Durante el ciclo de pulverización, la temperatura del lecho (por ejemplo, de 35°C a 45°C; o 40°C) se mantiene constante para evitar la humectación en

exceso. Una vez que se aplica toda la solución aglutinante necesaria, el material se seca adicionalmente hasta el valor de LOD (es decir pérdida por secado, por sus siglas en inglés) buscado (por ejemplo, por debajo de 1 %) antes de la descarga. La cantidad de aglutinante (por ejemplo, alcohol polivinílico) es entre 2 % y 6 % y en algunos casos de 3 %; y la concentración de la solución es entre 3 % y 7 %, y en algunos casos de 4,5 %. El tiempo del proceso de aglomeración para el lote de 60 kg es entre 45 minutos y 220 minutos y en algunos casos de 150 minutos. Una vez que el granulado está seco, el material se pasa a través de un tamiz de 1,4 y 2,00 mm para separar todas las partículas de mayor tamaño. Las partículas de mayor tamaño se pasan por el molino para reducirlas. Las partículas de mayor tamaño en general no exceden el 5 % de la producción total. Los materiales tamizados y molidos se colocan en un mezclador de cilindros (por ejemplo, un mezclador en V o un mezclador de tolva) y se agrega el lubricante (por ejemplo, behenato de glicerilo). El lubricante se tamiza y se agrega a los gránulos y se mezcla al número predeterminado de revoluciones o tiempo (por ejemplo, tiempo de mezcla de 5 min a 15 min y en algunos casos 10 min). El porcentaje de lubricante es entre 0,5 % y 4 %, y en algunos casos de 2 %. El nivel de lubricación se establece para una cobertura suficiente de la distribución de tamaño de partícula ya sea más grande o más pequeña. Otras características incluyen la densidad aparente (por ejemplo, de 0,3 g/ml a 0,8 g/ml y en algunos casos 0,5 g/ml), y el contenido de humedad (por ejemplo, no más de 1 %). El tamaño de partícula y el flujo de la mezcla final son factores para obtener un llenado uniforme de las cavidades en una compresora rotatoria. El flujo y la velocidad de rotación máxima de la compresora se ajustan (dependiendo del tipo/tamaño 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 través de un embudo a un dispositivo distribuidor para llenar las cavidades de la matriz que pasan por debajo de dicho dispositivo. Se hacen ajustes de peso para mantener el peso dentro del rango especificado, y se hacen ajustes a la regulación 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 0,5 %) del comprimido. Un espesor adecuado (con relación al área superficial total) y una menor friabilidad ayudan a reducir el daño del núcleo y la pérdida de principio activo durante el recubrimiento. Se toman muestras de los comprimido a intervalos predeterminados para controlar las especificaciones.

El recubrimiento del comprimido EA

Los núcleos de los comprimidos EA se pueden recubrir en una etapa. El recubrimiento EA se aplica directamente sobre la superficie de los núcleos de los comprimidos y actúa controlando la liberación de la sal de bupropion.

El recubrimiento EA es una capa semipermeable que comprende un polímero formador de película insoluble en agua y permeable al agua, un polímero soluble en agua y opcionalmente un plastificante.

Los ejemplos no limitantes de los polímeros formadores de película, insolubles en agua y permeable al agua útiles para el recubrimiento EA incluyen éteres de celulosa, ésteres de celulosa, alcohol polivinílico y sus mezclas. En ciertas realizaciones, los polímero formadores de película, insolubles en agua y permeables al agua son las etil celulosas y se pueden seleccionar entre las siguientes: etil celulosa grados PR100, PR45 PR20, PR10 y PR7 (Ethocel®, Dow) y sus combinaciones. En al menos una realización la etil celulosa grado PR100 es el polímero formador de película insoluble en agua y permeable al agua. La cantidad de polímero formador de película insoluble en agua y permeable al agua puede variar de 1 % a 8 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones la cantidad de polímero formador de película, insoluble en agua y permeable al agua es de 2 % a 6 % en peso del peso seco del comprimido. Para ciertas realizaciones de los comprimidos EA de 174 mg o de 348 mg de dosis de la invención, la cantidad de polímero formador de película, insoluble en agua y permeable al agua es de 1 % a 15 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones de los comprimidos EA de 174 mg de dosis, la cantidad de polímero formador de película, insoluble en agua y permeable al agua está presente en 10,5 % en peso del

peso seco del comprimido. En lo que se refiere al recubrimiento EA en sí, la cantidad de polímero formador de película, insoluble en agua y permeable al agua en ciertas realizaciones de los comprimidos EA de 174 mg de dosis es de 35 % a 60 % en peso del peso seco del recubrimiento EA. Por ejemplo, en ciertas realizaciones del comprimido EA de 174 mg de dosis, la cantidad de polímero insoluble en agua y permeable al agua presente es de 55 % en peso del peso seco del recubrimiento EA. Para ciertas realizaciones del comprimido EA de 348 mg de dosis de la invención, la cantidad de polímero formador de película, insoluble en agua y permeable al agua es de 1 % a 8 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones del comprimido de EA de 300 mg de dosis, la cantidad de polímero formador de película, insoluble en agua y permeable al agua presente es de 6,3 % en peso del peso seco del comprimido. En lo que se refiere al recubrimiento EA en sí, el polímero formador de película, insoluble en agua y permeable al agua en el comprimido EA de 300 mg de dosis puede estar presente en una cantidad de 55 % en peso del peso seco del recubrimiento EA.

En ciertas realizaciones, el recubrimiento EA contiene además un plastificante. Los ejemplos no limitantes de plastificantes que se pueden usar en el recubrimiento EA descrito aquí incluyen monoglicéridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicérido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de colza, aceite de oliva, aceite de sésamo, citrato de trietilo; alcoholes polihídricos, glicerol, glicerina, sorbitol, ésteres 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 epoxidado, trimelitato de triisoctilo, ftalato de dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, 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-

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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 mezclas, polioles (p. ej., polietilenglicol) de diversos pesos moleculares y sus mezclas. La cantidad de plastificante para el recubrimiento EA puede variar de 0,5 % a 4 % en peso del peso seco del comprimido. En otra realización de la invención, cuando se usa una mezcla de dos plastificantes, la relación de los dos plastificantes puede variar de 5:95 a 95:5. En al menos una realización de la invención, el plastificante es polietilenglicol 4000, sebacato de dibutilo o una mezcla de estos. La relación polietilenglicol 4000:sebacato de dibutilo puede variar de 5:95 a 95:5. Para ciertas realizaciones de los comprimidos EA de 174 mg de dosis de la invención, la cantidad de plastificante presente en el recubrimiento EA es de 0,5 % a 4 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones del comprimido EA de 174 mg de dosis, la cantidad de plastificante está presente en 3,1 % en peso del peso seco del comprimido. Para ciertas realizaciones del comprimido EA de 348 mg de dosis de la invención, la cantidad de plastificante presente es de 0,5 % a 3 % en peso del peso seco del comprimido. Por ejemplo, en ciertas realizaciones del comprimido EA de 348 mg de dosis, la cantidad de plastificante presente es de 2,0 % en peso del peso seco del comprimido. Para ciertas realizaciones de ambas formas farmacéuticas de 174 mg y 348 mg, el plastificante está presente en una cantidad entre 6 % y 30 % en peso del peso seco del recubrimiento EA. Por ejemplo, en ciertas realizaciones la cantidad de plastificante presente es de 17 % en peso del peso seco del recubrimiento EA.

Los ejemplos no limitantes de los polímeros solubles en agua útiles para el recubrimiento EA incluyen polivinilpirrolidona, hidroxipropilmetilcelulosa, hidroxipropilcelulosa y sus mezclas. En al menos una realización de la invención, el polímero soluble en agua es polivinilpirrolidona (por ejemplo, Povidona® USP) la cantidad del cual puede variar de 1,5 % a 10 % en peso del peso seco del comprimido. En lo que se refiere al

recubrimiento EA en sí, la cantidad de polímero soluble en agua presente puede variar de 20 % a 50 % en peso del peso seco del recubrimiento EA. Para ciertas realizaciones del comprimido EA de 174 mg de dosis de la invención, la cantidad de polímero soluble en agua presente es de 1,5 % a 10 % en peso del peso seco del comprimido o de 20 % a 50 % en peso del peso seco del recubrimiento EA. Por ejemplo, en ciertas realizaciones del comprimido EA de 174 mg de dosis, el polímero soluble en agua está presente en una cantidad de 28 % en peso del peso seco del recubrimiento EA. Para ciertas realizaciones del comprimido EA de 348 mg de dosis de la invención, la cantidad de polímero soluble en agua presente es de 1,5 % a 10 % del peso seco del comprimido y de 20 % a 50 % en peso del peso seco del recubrimiento EA. Por ejemplo, en ciertas realizaciones del comprimido EA de 300 mg de dosis, el polímero soluble en agua está presente en una cantidad de 28 % en peso del peso seco del recubrimiento EA.

La relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua para el recubrimiento del comprimido EA variará típicamente de 3:1:4 a 5:1:2. Por ejemplo, en ciertas realizaciones la relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua para el recubrimiento del comprimido EA es 4:1:3. En al menos una realización del recubrimiento del comprimido EA, la relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua es de 7:2:6 a 19:5:18 y en otras realizaciones es de 13:4:12.

La preparación y aplicación del recubrimiento EA pueden ser las siguientes. El polímero formador de película insoluble en agua y permeable al agua, (por ejemplo, etilcelulosa) y el plastificante (por ejemplo, polietilenglicol 4000, sebacato de dibutilo o una mezcla), se disuelven en un disolvente orgánico (por ejemplo, alcohol etílico). A continuación se agrega el polímero soluble en agua (por ejemplo, polivinilpirrolidona) hasta que se logra una mezcla homogénea. Después se pulveriza la solución de

recubrimiento de control de la liberación resultante sobre los núcleos de los comprimidos usando un equipo de lecho fluidizado revestidor de comprimidos o cualquier otro equipo de revestimiento adecuado conocido por los técnicos en la materia, hasta que se logra el aumento de peso deseado. Los núcleos de los comprimidos recubiertos con el recubrimiento EA se secan posteriormente antes de aplicar una barrera contra la humedad.

El técnico con experiencia apreciará que el control de la permeabilidad puede controlar la liberación de la sal de bupropion y/o la cantidad de recubrimiento aplicada a los núcleos de los comprimidos. La permeabilidad del recubrimiento EA, se puede alterar variando la relación polímero formador de película, insoluble en agua y permeable al agua:plastificante:polímero soluble en agua y/o la cantidad de recubrimiento aplicada al núcleo del comprimido. Se puede obtener una liberación más extendida con una cantidad mayor de polímero formador de película insoluble en agua y permeable al agua. El agregado de otros excipientes al núcleo del comprimido también puede alterar la permeabilidad del recubrimiento EA. Por ejemplo, si se desea que el núcleo del comprimido comprenda además un agente de expansión, la cantidad de plastificante en el recubrimiento de control de la liberación se debe aumentar para hacer el recubrimiento más flexible puesto que la presión ejercida en un recubrimiento menos flexible por el agente de expansión podría romper el recubrimiento. Además, la proporción de polímero formador de película, insoluble en agua y permeable al agua y de polímero soluble en agua también se puede alterar dependiendo de si se desea un perfil de disolución y/o liberación más rápido o más lento.

Dependiendo del perfil de disolución o de liberación in vivo deseado, el aumento de peso después de recubrir el núcleo del comprimido con el recubrimiento EA puede variar de 3 % a 30 % del peso del núcleo del comprimido seco. Para ciertas realizaciones del comprimido EA de 174 mg de dosis de la invención el aumento de peso es de 8 % a 20 % del peso del núcleo del comprimido seco. Por ejemplo, en ciertas realizaciones del comprimido de EA de 174 mg de dosis, el aumento de peso es 14 % del peso del núcleo del comprimido seco. Para ciertas realizaciones

del comprimido EA de 348 mg de dosis de la invención el aumento de peso es de 10 % a 15 % del peso del núcleo del comprimido seco. Por ejemplo, en ciertas realizaciones del comprimido EA de 348 mg de dosis, el aumento de peso es 13 % del peso del núcleo del comprimido seco.

El comprimido EA de la invención proporciona una absorción mejorada de la sal de 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 después de 2 horas, se libera no más de 25 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera de 10 % a 20 % del contenido de bromhidrato de bupropion después de 2 horas. Después de 4 horas, se libera de 25 % a 55 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera de 30 % a 50 % del contenido de bromhidrato de bupropion después de 4 horas. Después de 8 horas, se libera más de 60 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera de 70 % a 90 % del contenido de bromhidrato de bupropion después de 8 horas. Después de 16 horas se libera más de 70 % del contenido de bromhidrato de bupropion. Por ejemplo, en ciertas realizaciones se libera más de 80 % del contenido de bromhidrato de bupropion después de 16 horas.

Además en algunas realizaciones la invención proporciona fomulaciones de absorción mejorada donde no más de 40 % se libera después de 2 horas (por ejemplo, 33 %); después de 4 horas se libera de 40 a 75 % (por ejemplo, 59 %); después de 8 horas se libera al menos 75 % (por ejemplo, 91 %); y después de 16 horas se libera al menos 85 % (por ejemplo, 97 %).

Matriz de liberación controlada

En otras realizaciones de la presente invención, se proporciona una matriz de liberación controlada cuya cinética de liberación del fármaco desde el núcleo de la matriz es dependiente al menos en parte de las propiedades de difusión y/o de erosión de los excipientes dentro de la composición. En esta realización las matrices de liberación controlada contienen una cantidad

eficaz de una sal de bupropion y al menos un excipiente farmacéuticamente aceptable. La cantidad de sal de bupropion presente en la matriz de liberación controlada puede variar entre 40 % y 90 % en peso del peso seco del comprimido de matriz. Por ejemplo, en ciertas realizaciones el bromhidrato de bupropion está presente en una cantidad de 60 % a 80 %, y en otra realización en 70 % en peso del peso seco del comprimido de matriz. La matriz de liberación controlada puede ser multiparticulada o uniparticulada y se puede recubrir con al menos un recubrimiento funcional o no funcional, o un recubrimiento de liberación inmediata que contiene una sal de bupropion u otro fármaco. Los recubrimientos funcionales incluyen a modo de ejemplo recubrimientos poliméricos de liberación controlada, recubrimientos poliméricos entéricos y similares. Los recubrimientos no funcionales son recubrimientos que no afectan a la liberación del fármaco pero que afectan a otras propiedades (por ejemplo, pueden mejorar la química, la biología o el aspecto físico de la formulación de liberación controlada). Los técnicos con experiencia en el área farmacéutica y el diseño de medicamentos están al tanto de las matrices de liberación controlada que se utilizan convencionalmente en las composiciones farmacéuticas orales adoptadas para la liberación controlada y de los medios para su preparación. Se describen ejemplos de matrices de liberación controlada en las patentes de Estados Unidos N° 6,326,027; 6,340,475; 6,905,709; 6,645,527; 6,576,260; 6,326,027; 6,254,887; 6,306,438; 6,129,933; 5,891,471; 5,849,240; 5,965,163; 6,162,467; 5,567,439; 5,552,159; 5,510,114; 5,476,528; 5,453,283; 5,443,846; 5,403,593; 5,378,462; 5,350,584; 5,283,065; 5,273,758; 5,266,331; 5,202,128; 5,183,690; 5,178,868; 5,126,145; 5,073,379; 5,023,089; 5,007,790; 4,970,075; 4,959,208; 4,59,208; 4,861,598; 4,844,909; 4,834,984; 4,828,836; 4,806,337; 4,801,460; 4,764,378; 4,421,736; 4,344,431; 4,343,789; 4,346,709; 4,230,687; 4,132,753; 5,591,452; 5,965,161; 5,958,452; 6,254,887; 6,156,342; 5,395,626; 5,474,786; y 5,919,826.

Los excipientes adecuados para usar en dichas matrices de liberación controlada incluyen, a modo de ejemplo, materiales resistentes a la liberación o de liberación controlada como polímeros hidrófobos, polímeros

hidrófilos, materiales lipófilos y sus mezclas. Los ejemplos no limitantes de componentes hidrófobos o lipófilos incluyen monoestearato de glicerilo, mezclas de monoestearato de glicerilo y monopalmitato de glicerilo (Myvaplex, Eastman Fine Chemical Company), monooleato de glicerilo, una mezcla de mono, di y triglicéridos (ATMUL 84S), monolaurato de glicerilo, parafina, cera blanca, ácidos carboxílicos de cadena larga, ésteres de ácidos carboxílicos de cadena larga, alcoholes de ácidos carboxílicos de cadena larga y sus mezclas. Los ácidos carboxílicos de cadena larga pueden contener de 6 a 30 átomos de carbono; en ciertas realizaciones al menos 12 átomos de carbono, y en otras realizaciones de 12 a 22 átomos de carbono. En algunas realizaciones esta cadena carbonada está totalmente saturada y no es ramificada, mientras otras contienen uno o más enlaces dobles. En al menos una realización los ácidos carboxílicos de cadena larga contienen anillos de 3 carbonos o grupos hidroxilo. Los ejemplos no limitantes de ácidos saturados de cadena lineal incluyen ácido n-dodecanoico, ácido n-tetradecanoico, ácido n-hexadecanoico, ácido caproico, ácido caprílico, ácido cáprico, ácido láurico, ácido mirístico, ácido palmítico, ácido esteárico, ácido araquídico, ácido behénico, ácido montánico y ácido melísico. También son útiles los ácidos monocarboxílicos insaturados monoolefínicos de cadena lineal. Los ejemplos no limitantes de éstos incluyen ácido oleico, ácido gadoleico y ácido erúcico. También son útiles los ácidos monocarboxílicos insaturados (poliolefínicos) de cadena lineal. Los ejemplos no limitantes de éstos incluyen ácido linoleico, ácido linolénico, ácido araquidónico y ácido behenólico. Los ácidos ramificados útiles incluyen, por ejemplo, ácido diacetiltartárico. Los ejemplos no limitantes de ésteres de ácidos carboxílicos de cadena larga incluyen monoestearatos de glicerilo; monopalmitatos de glicerilo; mezclas de monoestearato de glicerilo y monopalmitato de glicerilo (Myvaplex 600, Eastman Fine Chemical Company); monolinoleato de glicerilo; monooleato de glicerilo; mezclas de monopalmitato de glicerilo, monoestereato de glicerilo, monooleato de glicerilo y monolinoleato de glicerilo (Myverol 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, monolinolenato de glicerilo y monogadoleato de glicerilo (Myverol 18-99, Eastman Fine Chemical Company); glicéridos acetilados como monoglicéridos acetilados destilados (Myvacet 5-07, 7-07 y 9-45, Eastman Fine Chemical Company); mezclas de monoésteres de propilenglicol, monoglicéridos destilados, estearoil lactilato de sodio y dióxido de silicio (Myvatex TL, Eastman Fine Chemical Company); mezclas de monoésteres de propilenglicol, monoglicéridos destilados, estearoil lactilato de sodio y dióxido de silicio (Myvatex TL, Eastman Fine Chemical Company) d-alfa tocoferil polietilenglicol 1000 succinato (Vitamina E TPGS, Eastman Chemical Company); mezclas de ésteres de mono y diglicéridos como Atmul (Humko Chemical Division de Witco Chemical); estearoil lactilato de calcio; mono y diglicéridos etoxilados; mono y diglicéridos lactados; éster lactilato de ácido carboxílico de glicerol y propilenglicol; ésteres lactílicos de ácidos carboxílicos de cadena larga; ésteres de poliglicerol de ácidos carboxílicos de cadena larga, mono y diésteres de propilenglicol de ácidos carboxílicos de cadena larga; estearoil lactilato de sodio; monoestearato de sorbitán; monooleato de sorbitán; otros ésteres de sorbitán de ácidos carboxílicos de cadena larga; monoglicéridos succinilados; citrato de estearil monoglicerilo; heptanoato de estearilo; ésteres cetílicos de ceras; octanoato de cetearilo; ésteres C10-C30 de colesterol/lavosterol; ésteres de sacarosa de ácidos carboxílicos de cadena larga; y sus mezclas.

Los alcoholes útiles como excipientes para las matrices de liberación controlada pueden incluir las formas hidroxilo de los ácidos carboxílicos ejemplificados antes y también el alcohol cetearílico.

Además, las ceras pueden ser útiles solas o en combinación con los materiales mencionados antes, como excipientes para las realizaciones de matrices de liberación controlada de la presente invención. Los ejemplos no limitantes de estos incluyen cera blanca, parafina, cera microcristalina, cera carnauba y sus mezclas.

El agente lipófilo puede estar presente en una cantidad entre 5 % y 90 % en peso de la forma farmacéutica de matriz de liberación controlada. Por ejemplo, en ciertas realizaciones el agente lipófilo está presente en una cantidad entre 10 % y 85 %, y en otras realizaciones entre 30 % y 60 % en peso de la forma farmacéutica de matriz de liberación controlada.

Los ejemplos no limitantes de polímeros hidrófilos que se pueden usar en ciertas realizaciones de la forma farmacéutica de matriz de liberación controlada incluyen hidroxipropilmetilcelulosa (HPMC), hidroxipropilcelulosa (HPC), hidroxietilcelulosa (HEC), carboximetilcelulosa (CMC) u otros éteres de celulosa, polioxietileno, ácido algínico, derivados del ácido acrílico como ácido poliacrílico, Carbopol (B.F. Goodrich, Cleveland, Ohio), polímero de polimetacrilato como Eudragit® RL, RS, R, S, NE y E (Rhome Pharma, Darmstadt, Alemania), polímero del ácido acrílico, polímero del ácido metacrílico, polímero del hidroxietil metacrilato (HEMA), polímero de hidroximetil metacrilato (HMMA), alcoholes polivinílicos.

El polímero hidrófilo puede estar presente en una cantidad entre 10 % y 90 % en peso de la forma farmacéutica de matriz de liberación controlada. Por ejemplo, en ciertas realizaciones el polímero hidrófilo está presente en una cantidad entre 20 % y 75 %, y en otras realizaciones entre 30 % y 60 % en peso de la forma farmacéutica de matriz de liberación controlada.

En al menos una realización, la forma farmacéutica de matriz de liberación controlada comprende hidroxipropilmetilcelulosa (HPMC). La HPMC es una anhidroglucosa en la cual algunos de los grupos hidroxilo se sustituyen con grupos metilo para formar porciones éter metílico, y otros se sustituyen con grupos hidroxipropilo o con grupos metoxipropilo para formar porciones éter hidroxipropílico o éter metoxipropílico. Los ejemplos no limitantes de hidroxipropilmetilcelulosas que están comercialmente disponibles incluyen METHOCEL® E (tipo USP 2910), METHOCEL® F (tipo USP 2906), METHOCEL® J (tipo USP 1828), METHOCEL® K (tipo USP 2201) y METHOCEL® serie 310, productos de The Dow Chemical Company, Midland, Mich., EE.UU. El grado promedio de sustitución

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con metoxilo en estos productos puede variar de 1,3 a 1,9 (de las tres posiciones en cada unidad del polímero de celulosa que están disponibles para sustitución) mientras el grado promedio de sustitución con hidroxipropilo por unidad expresada en términos molares puede variar de 0,13 a 0,82. La forma farmacéutica puede comprender los diferentes grados de HPMC que tienen diferentes viscosidades. El tamaño de un polímero de HPMC se expresa no como el peso molecular sino en términos de su viscosidad como una solución al 2 % en peso en agua. Los diferentes grados de HPMC se pueden combinar para lograr las características deseadas de viscosidad. Por ejemplo, el al menos un polímero farmacéuticamente aceptable puede comprender dos polímeros de HPMC como por ejemplo Methocel® K3 LV (que tiene una viscosidad de 3 cp) y Methocel® K100M CR (que tiene una viscosidad de 100.000 cp). Además, el polímero puede comprender dos formas hidroxipropilcelulosa como Klucel® LF y Klucel® EF. Además, el al menos un polímero puede comprender una mezcla de un Klucel® y un Methocel®.

En al menos una realización la forma farmacéutica de matriz de liberación controlada comprende un óxido de polietileno (OPE). El óxido de polietileno es un polímero lineal de óxido de etileno sin sustituir. En ciertas realizaciones se usan los polímeros poli(óxido de etileno) que tienen viscosidad-pesos moleculares promedio de 100.000 daltons y mayores. Los ejemplos no limitantes de poli(óxido de etileno) que están comercialmente disponibles incluyen: POLYOX® NF, grado WSR coagulante, peso molecular 5 millones; POLYOX® grado WSR 301, peso molecular 4 millones; POLYOX® grado WSR 303, peso molecular 7 millones; POLYOX® grado WSR N-60K, peso molecular 2 millones; y sus mezclas. Estos polímeros 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 OPE se puede obtener mezclando OPE de pesos moleculares diferentes que están disponibles comercialmente.

En al menos una realización de la forma farmacéutica de matriz de liberación controlada, se combinan OPE y HPMC dentro de la misma matriz de liberación controlada. En

ciertas realizaciones, los poli(óxido de etileno) tienen pesos moleculares que varían de 2.000.000 a 10.000.000 Da. Por ejemplo, en al menos una realización los óxidos de polietileno tienen pesos moleculares que varían de 4.000.000 a 7.000.000 Da. En ciertas realizaciones los polímeros de HPMC tienen una viscosidad dentro del rango de 4.000 centipoise a 200.000 centipoise. Por ejemplo, en al menos una realización los polímeros de HPMC tienen una viscosidad entre 50.000 centipoise y 200.000 centipoise y en otras realizaciones entre 80.000 centipoise y 120.000 centipoise. Las cantidades relativas de OPE y HPMC dentro de la matriz de liberación controlada pueden variar dentro del alcance de la invención. En al menos una realización la relación de pesos OPE:HPMC es de 1:3 a 3:1. Por ejemplo, en ciertas realizaciones la relación de pesos OPE:HPMC es de 1:2 a 2:1. En cuanto a la cantidad total de polímero con relación a toda la matriz, esto también puede variar y puede depender de la concentración de fármaco deseada. En al menos una realización la cantidad total de polímero en la matriz puede constituir de 15 % a 90 % en peso de la forma farmacéutica de matriz. Por ejemplo, en ciertas realizaciones la cantidad total de polímero en la matriz es de 20 % a 75 %, en otras realizaciones de 30 % a 60 % y aún en otras realizaciones de 10 % a 20 % en peso de la forma farmacéutica de matriz.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende un polímero hidrófobo como la etilcelulosa. La viscosidad de la etilcelulosa se puede seleccionar para influir en la velocidad de liberación del fármaco. En ciertas realizaciones la etilcelulosa tiene una viscosidad de 7 a 100 cP (cuando se mide como una solución al 5 % a 25°C en un viscosímetro Ubbelohde, usando un disolvente 80:20 tolueno:etanol). En ciertas realizaciones el polímero hidrófobo puede constituir de 10 % a 90 % en peso de la forma farmacéutica de matriz. Por ejemplo, en al menos una realización el polímero hidrófobo constituye de 20 % a 75 % y en otras realizaciones de 30 % a 60 % en peso de la forma farmacéutica de matriz.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende

al menos un aglutinante. En ciertas realizaciones el aglutinante es insoluble en agua. Los ejemplos de aglutinantes incluyen aceite vegetal hidrogenado, aceite de ricino, parafina, alcoholes alifáticos superiores, ácidos alifáticos superiores, ácidos grasos de cadena larga, ésteres de ácidos grasos, materiales similares a cera como alcoholes grasos, ésteres de ácidos grasos, glicéridos de ácidos grasos, grasas hidrogenadas, hidrocarburos, ceras normales, ácido esteárico, alcohol estearílico, polímeros hidrófobos e hidrófilos que tienen esqueletos hidrocarbonados y sus mezclas. Los ejemplos no limitantes de polímeros aglutinantes solubles en agua incluyen almidón modificado, gelatina, polivinilpirrolidona, derivados de celulosa (como por ejemplo hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa (HPC)), alcohol polivinílico y sus mezclas. En al menos una realización, el aglutinante puede estar presente en una cantidad entre 0,1 % y 20 % en peso de la forma farmacéutica de matriz. Por ejemplo, en ciertas realizaciones el aglutinante está presente en una cantidad entre 0,5 % y 15 %, y en otras realizaciones entre 2 % y 10 % en peso de la forma farmacéutica de matriz.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende al menos un lubricante. Los ejemplos no limitantes de lubricantes incluyen ácido esteárico, aceites vegetales hidrogenados (como aceite de semilla de algodón hidrogenado (Sterotex®), aceite de soja hidrogenado (Sterotex® HM) y aceite de soja hidrogenado y cera de ricino (Sterotex® K)), alcohol estearílico, leucina, polietilenglicol (PM 1.450, adecuadamente 4.000 y mayor), estearato de magnesio, monoestearato de glicerilo, ácido esteárico, behenato de glicerilo, polietilenglicol, polímeros de óxido de etileno (por ejemplo, los disponibles bajo la marca registrada Carbowax® de Union Carbide, Inc., Danbury, Conn.), lauril sulfato de sodio, lauril sulfato de magnesio, oleato de sodio, estearil fumarato de sodio, DL-leucina, sílice coloidal y sus mezclas. El lubricante puede estar presente en una cantidad entre 0 % y 4 % en peso de la matriz sin recubrir comprimida. Por ejemplo, en ciertas realizaciones el lubricante está presente en una cantidad

entre 0 % y 2,5 % en peso de la matriz sin recubrir comprimida.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende un plastificante. Los ejemplos no limitantes de plastificantes incluyen sebacato de dibutilo, ftalato de dietilo, citrato de trietilo, citrato de tributilo, triacetina, ésteres del ácido cítrico como citrato de trietilo NF XVI, citrato de tributilo, ftalato de dibutilo, 1,2-propilenglicol, polietilenglicoles, propilenglicol, ftalato de dietilo, aceite de ricino, monoglicéridos acetilados, ésteres de ftalato y sus mezclas. En al menos una realización, el plastificante puede estar presente en una cantidad entre 1 % y 70 % en peso del polímero de liberación controlada en la forma farmacéutica de matriz. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad entre 5 % y 50 % y en otras realizaciones entre 10 % y 40 % en peso del polímero de liberación controlada en la forma farmacéutica de matriz.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende al menos un diluyente, cuyos ejemplos no limitantes incluyen fosfato dicálcico, sulfato de calcio, lactosa o sacarosa u otros disacáridos, celulosa, derivados de celulosa, caolín, manitol, almidón seco, glucosa u otros monosacáridos, dextrina u otros polisacáridos, sorbitol, inositol, sucralfato, hidroxiapatita cálcica, fosfatos de calcio y sales de ácido graso como estearato de magnesio. En ciertas realizaciones el diluyente se puede agregar en una cantidad para que la combinación del diluyente y la sustancia activa comprenda hasta 60 % y en otras realizaciones hasta 50 %, en peso de la composición.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende un solubilizante. El solubilizante puede actuar para aumentar la solubilidad instantánea de la sal de bupropion. El solubilizante se puede seleccionar entre los tensioactivos hidrófilos o los tensioactivos lipófilos o sus mezclas. Los tensioactivos pueden ser tensioactivos aniónicos, no iónicos, catiónicos y

zwiteriónicos. Los tensioactivos hidrófilos no iónicos se pueden seleccionar del grupo compuesto, pero no exclusivamente, de: ésteres de ácidos grasos de polietilenglicol sorbitán y productos hidrófilos de transesterificación de un poliol con al menos un miembro del grupo de los triglicéridos, los aceites vegetales y aceites vegetales hidrogenados como glicerol, etilenglicol, polietilenglicol, sorbitol, propilenglicol, pentaeritritol o un sacárido, d-α-tocoferilo polietilenglicol 1.000 succinato. Los tensioactivo iónicos se pueden seleccionar del grupo compuesto, pero no exclusivamente, de: sales de alquilamonio; sales de ácido fusídico; derivados de ácidos grasos de aminoácidos, oligopéptidos y polipéptidos; derivados glicéridos de aminoácidos, oligopétidos y polipéptidos; lecitinas y lecitinas hidrogenadas; lisolecitinas y lisolecitinas hidrogenadas; fosfolípidos y sus derivados; lisofosfolípido y sus derivados; sales de ésteres de ácidos grasos de carnitina; sales de alquilsulfatos; sales de ácidos grasos; docusato de sodio; lactilatos de acilo; ésteres de ácido tartárico mono y diacetilados de mono y diglicéridos; mono y diglicéridos succinilados; ésteres de ácido cítrico de mono y diglicéridos; y sus mezclas. Los tensioactivos lipófilos se pueden seleccionar del grupo compuesto, pero no exclusivamente, de: alcoholes grasos; ésteres de ácidos grasos del glicerol; ésteres de ácidos grasos de glicerol acetilado; ésteres de ácidos grasos de alcoholes inferiores; ésteres de ácidos grasos de propilenglicol; ésteres de ácidos grasos de sorbitán; ésteres de ácidos grasos de polietilenglicol sorbitán; esteroles y derivados del esterol; esteroles y derivados del esterol polioxietilados; éteres alquílicos de polietilenglicol; ésteres de azúcares; éteres de azúcares; derivados del ácido láctico de mono y diglicéridos; productos hidrófobos de transesterificación de un poliol con al menos un miembro del grupo de los glicéridos, aceites vegetales, aceites vegetales hidrogenados, ácidos grasos y esteroles; vitaminas liposolubles/derivados de vitaminas; ésteres de ácidos grasos de PEG sorbitán, ésteres de ácidos grasos de PEG glicerol, ácidos grasos poliglicerizados, copolímeros en bloque de polioxietileno-polioxipropileno, ésteres de ácidos grasos de sorbitán; y sus mezclas. En al menos una realización

el solubilizante se puede seleccionar entre: estearato de PEG-20-glicerilo (Capmul® de Abitec), aceite de ricino hidrogenado PEG-40 (Cremophor RH 40® de BASF), aceite de maíz PEG-6 (Labrafil® de Gattefosse), lauril macrogol 32 glicérido (Gelucire44/14® de Gattefosse) estearoil macrogol glicérido (Gelucire50/13® de Gattefosse), mono dioleato de poliglicerilo 10 (Caprol® PEG860 de Abitec), oleato de propilenglicol (Lutrol® de BASF), dioctanoato de propilenglicol (Captex® de Abitec), caprilato/caprato de propilenglicol (Labrafac® de Gattefosse), monooleato de glicerilo (Peceol® de Gattefosse), monolinoleato de glicerol (Maisine® de Gattefosse), monoestearato de glicerol (Capmul® de Abitec), monolaurato de sorbitán PEG-20 (Tween20® de ICI), lauril éter PEG-4 (Brij30® de ICI), diestearato de sacarosa (Sucroester7® de Gattefosse), monopalmitato de sacarosa (Sucroester15® de Gattefosse), copolímero en bloque de polioxietileno-polioxipropileno (serie Lutrol® de BASF), hidroxiestearato de polietilenglicol 660, (Solutol® 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, betaínas, polietilenglicol (Carbowax® de DOW), d-α-tocoferil polietilenglicol 1.000 succinato, (Vitamina E TPGS® de Eastman) y sus mezclas. En al menos otra realización el solubilizante se puede seleccionar entre aceite de ricino hidrogenado PEG-40 (Cremophor RH 40® de BASF), lauril macrogol-32 glicérido (Gelucire 44/14® de Gattefosse) estearoil macrogol glicérido (Gelucire50/13® de Gattefosse), monolaurato de sorbitán PEG-20 (Tween20® de ICI), lauril éter PEG-4 (Brij30® de ICI), copolímero en bloque de polioxietileno-polioxipropileno (serie Lutrol® de BASF), lauril sulfato de sodio, dodecil sulfato de sodio, polietilenglicol (Carbowax® de DOW) y sus mezclas.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende un potenciador del hinchamiento. Los potenciadores del hinchamiento son integrantes de una categoría especial de excipientes que se hinchan rápidamente en gran medida y dan lugar a un aumento del tamaño del comprimido. A menores concentraciones, estos excipientes se pueden usar

como super desintegrantes; sin embargo a concentraciones por encima de 5 % p/p estos agentes pueden actuar como potenciadores del hinchamiento y ayudar a aumentar el tamaño de la forma farmacéutica de matriz. De acuerdo con ciertas realizaciones de las formas farmacéuticas de matriz de la invención, los ejemplos de potenciadores del hinchamiento incluyen pero no exclusivamente: hidroxipropilcelulosa poco sustituida, celulosa microcristalina, carboximetilcelulosa sódica o cálcica reticulada, fibra de celulosa, polivinilpirrolidona reticulada, ácido poliacrílico reticulado, resina Amberlite reticulada, alginatos, silicato de magnesio-aluminio coloidal, gránulos de almidón de maíz, gránulos de almidón de arroz, gránulos de almidón de papa, almidón pregelatinizado, carboximetil almidón sódico y sus mezclas. En al menos una realización de las formas farmacéuticas de matriz, el potenciador de hinchamiento es polivinilpirrolidona reticulada. El contenido del potenciador de hinchamiento puede ser de 5 % a 90 % en peso de la forma farmacéutica de matriz. Por ejemplo, en ciertas realizaciones el potenciador de hinchamiento está presente en una cantidad entre 10 % y 70 %, y en otras realizaciones entre 15 % y 50 % en peso de la forma farmacéutica de matriz.

En al menos una realización de la invención la forma farmacéutica de matriz de liberación controlada comprende aditivos para permitir que el agua penetre en el núcleo de la preparación (de aquí en adelante denominada "base hidrófila"). En ciertas realizaciones, la cantidad de agua requerida para disolver 1 g de la base hidrófila no es más de 5 ml, y en otras realizaciones no es más de 4 ml a la temperatura de 20°C ± 5°C. Cuanto mayor la solubilidad de la base hidrófila en agua, más eficaz es la base en permitir que el agua penetre en el núcleo de la preparación. La base hidrófila incluye, entre otros, polímeros hidrófilos como 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 azúcares como D-sorbitol, xilitol o similares, azúcares como sacarosa, maltosa anhidra, D-fructosa, dextrano (por ejemplo, dextrano 40), glucosa o similares, tensioactivos como polioxietileno-aceite de

ricino hidrogenado (HCO; por ejemplo, Cremophor RH40 producido por BASF, HCO-40 y HCO-60 producido por Nikko Chemicals Co.), polioxietileno-polioxipropilenglicol (por ejemplo, Pluronic F68 producido por Asahi Denka Kogyo K.K.), ésteres de polioxietileno-sorbitán de ácidos grasos de alto peso molecular (Tween; por ejemplo, Tween 80 producido por Kanto Kagaku K.K.) o similares; sales como cloruro de sodio, cloruro de magnesio o similares; ácidos orgánicos como ácido cítrico, ácido tartárico o similares; aminoácidos como glicina, beta-alanina, clorhidrato de lisina o similares; y amino azúcares como meglumina. En al menos una realización la base hidrófila es PEG6000, PVP, D-sorbitol o sus mezclas.

En otra realización de la invención la forma farmacéutica de matriz de liberación controlada comprende al menos un desintegrante. Los ejemplos no limitantes de desintegrantes para usar en la forma farmacéutica de matriz incluyen croscarmelosa sódica, crospovidona, ácido algínico, alginato de sodio, ácido metacrílico-DVB, PVP reticulada, celulosa microcristalina, polacrilina potásica, glicolato de almidón sódico, almidón, almidón pregelatinizado y similares. En al menos una realización el desintegrante se selecciona entre polivinilpirrolidona reticulada (por ejemplo, Kollidon® CL), carboximetilcelulosa sódica reticulada (por ejemplo, Ac-Di-Sol), almidón o derivados de almidón como glicolato de almidón sódico (por ejemplo, Explotab®), o combinaciones con almidón (por ejemplo, Primojel™), resinas de intercambio iónico hinchables, como Amberlite IRP 88, formaldehido-caseína (por ejemplo, Esma Spreng™) y sus mezclas. En al menos una realización el desintegrante es glicolato de almidón sódico. El desintegrante puede estar presente en una cantidad entre 0 y 20 % del peso total de la matriz.

Las matrices de liberación controlada de la presente invención pueden contener además uno o más excipientes farmacéuticamente aceptables como, auxiliares o agentes de granulación, colorantes, aromatizantes, ajustadores del pH, antiadherentes, deslizantes y excipientes similares convencionalmente usados en las composiciones farmacéuticas.

En al menos una realización de la invención que comprende polímeros hinchables con agua formulados dentro de la matriz, la cinética de liberación de la sal de bupropion desde la matriz depende de la magnitud relativa de la velocidad de hinchamiento del polímero en el frente móvil gomoso/vítreo y la velocidad de erosión del polímero en el frente de polímero hinchado/medio de disolución. La cinética de liberación para la liberación de la sal de bupropion desde la matriz se puede aproximar con la ecuación siguiente:

$M_t/M_T=kt^n$

donde t es tiempo,

M_t es la cantidad de agente farmacéutico que se liberó en el tiempo t,

M_T es la cantidad total de agente farmacéutico contenido en la matriz,

k es una constante y

n es el exponente de la cinética de liberación

Esta ecuación es válida siempre que n siga siendo casi constante. Cuando n es igual a uno, la liberación del agente farmacéutico desde la matriz tiene una cinética de orden cero. Entonces, la cantidad de agente farmacéutico liberado es directamente proporcional al tiempo.

Cuando el proceso de hinchamiento del polímero elegido para el excipiente es el proceso principal que controla la liberación del fármaco (en comparación con la erosión del polímero hinchado), puede resultar una cinética de liberación de órden distinto de cero. En general, estas cinéticas de liberación establecen un valor de n que se acerca a 0,5, conduciendo a cinéticas de liberación del tipo Fickian de raíz cuadrada.

En al menos una realización de la invención, los polímeros que se van a incluir en la formulación se seleccionan para lograr una cinética de orden cero. La cinética de liberación de la matriz también puede ser establecida por el agente farmacéutico mismo. Un fármaco que es sumamente soluble puede tender a ser liberado más rápido que los fármacos que tienen solubilidad baja. Cuando un fármaco tiene solubilidad alta, el hinchamiento y la erosión del polímero deben tener lugar rápidamente para mantener una cinética de liberación de orden cero.

Si el hinchamiento y la erosión tienen lugar demasiado lentamente, el proceso de hinchamiento del polímero es el proceso principal que controla la liberación del fármaco (puesto que la droga difundirá del polímero hinchado antes de que el polímero se erosione). En esta situación, puede resultar una cinética de liberación de orden distinto de cero. Como resultado, la administración de un agente farmacéutico muy soluble requiere un excipente que se hinche y erosione relativamente rápido. Usar tal material para producir una matriz que durará 24 horas puede requerir una matriz grande. Para superar esta dificultad, se puede usar una matriz con forma de rosquilla con un orificio en el medio con un polímero que hincha y erosiona menos rápidamente. Con una matriz como esa, el área superficial de la matriz aumenta a medida que la matriz se erosiona. Esto expone más polímero, dando lugar a más hinchamiento y erosión del polímero a medida que la matriz encoge de tamaño. Este tipo de matriz también se puede usar con agentes farmacéuticos muy altamente solubles para mantener una cinética de liberación de orden cero.

En al menos otra realización de la invención, se puede lograr una cinética de liberación de orden cero controlando el área superficial de la forma farmacéutica de matriz que se expone a la erosión. Cuando se permite que el agua difunda en una composición de la matriz polimérica se obtiene una liberación de orden cero cuando la velocidad de liberación es regida o controlada mediante erosión de un área superfical constante por unidad de tiempo. Para asegurar que la erosión de la composición de la matriz polimérica sea el mecanismo de liberación predominante, es útil proporcionar una composición de la matriz polimérica que tenga propiedades que aseguren que la velocidad de difusión del agua en la composición de la matriz polimérica se corresponde prácticamente con la velocidad de disolución de la composición de la matriz polimérica en el medio acuoso. Por lo tanto, ajustando la naturaleza y la cantidad de constituyentes en la composición de la matriz polimérica se puede lograr un mecanismo de liberación de orden cero. Las composiciones empleadas se recubren de tal manera que al menos una superficie está expuesta al medio acuoso y esta superficie tiene un área superficial prácticamente

constante o controlada durante la erosión. En el presente contexto área superficial controlada se relaciona con un área superficial predeterminada pronosticada habitualmente a partir de la forma del recubrimiento del sistema de dosificación. Puede tener una forma cilíndrica uniforme simple o la forma cilíndrica puede tener uno o más extremos de sección decreciente para disminuir (o aumentar) el período de liberación inicial. En consecuencia, estas realizaciones proporcionan un método para controlar la liberación de una sal de bupropion en un medio acuoso mediante erosión de al menos una superficie de una composición farmacéutica que comprende: (i) una composición de la matriz que comprende (a) un polímero o una mezcla de polímeros, (b) una sal de bupropion y, opcionalmente, (c) uno o más excipientes farmacéuticamente aceptables y (ii) un recubrimiento que tiene al menos una abertura que expone una superficie de dicha matriz; donde el recubrimiento comprende: (a) un primer derivado de celulosa que tiene propiedades termoplásticas y que es prácticamente insoluble en el medio acuoso en el que se usará la composición, y al menos uno de (b) un segundo derivado de celulosa que es soluble o dispersable en agua, (c) opcionalmente un plastificante y (d) un relleno, donde el método comprende ajustar la concentración 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 la matriz corresponda a 100 % ± 30 % como, por ejemplo a 100 % ± 25 %, 100 % ± 20 %, 100 % ± 15 % o 100 % ± 10 %, o 100 % de la velocidad de disolución de la composición de la matriz para obtener una liberación de orden cero de al menos 60 % p/p como, por ejemplo al menos 65 % p/p, al menos 70 % p/p, al menos 75 % p/p, al menos 80 % p/p, al menos 85 % p/p, al menos 90 % p/p, al menos 95 % p/p o al menos 97 % a 98 % p/p de la sal de bupropion desde la composición farmacéutica cuando se la somete a una prueba de disolución in vitro.

En al menos otra realización de la invención, se acerca a una liberación del fármaco de orden cero mediante el uso de: (a) un núcleo de depósito que comprende la sal de bupropion y que tiene forma geométrica definida, (b) una plataforma de soporte aplicada a dicho núcleo de depósito

y que se caracteriza porque dicho núcleo de depósito contiene, mezclado con la sal de bupropion, un material polimérico con un grado alto de hinchamiento en contacto con agua o líquidos acuosos, un material polimérico gelificable, donde dichos materiales poliméricos son reemplazables por un único material polimérico que tiene propiedades tanto de hinchamiento como de gelificación, y otros adyuvantes capaces de proporcionar la mezcla con características adecuadas para su compresión y para su entrada de agua, donde dicha plataforma de soporte comprende un material polimérico insoluble en líquidos acuosos y recubre parcialmente dicho núcleo de depósito.

Estas y otras características y ventajas del sistema de acuerdo con ciertas realizaciones de la forma farmacéutica de matriz serán más evidentes a partir de la descripción detallada de las realizaciones preferidas de la invención que se indican de aquí en adelante a modo de ejemplo no limitante. El núcleo de depósito se puede obtener en general mediante compresión de la mezcla que contiene la sal de bupropion a una presión entre 1.000 y 4.000 kg/cm^2, para adquirir por lo tanto una forma geométrica definida. Los materiales poliméricos que tienen un grado de hinchamiento alto en general pueden ser polímeros insolubles reticulados, mientras que los materiales poliméricos gelificables son solubles y pueden controlar la entrada de agua.

La plataforma de recubrimiento comprende un material polimérico insoluble en agua y opcionalmente insoluble en líquidos biológicos biodegradables y capaz de mantener sus características de impermeabilidad al menos hasta la transferencia completa de la sal de bupropion contenida en el núcleo de depósito. Se aplica a una parte de la superficie externa del núcleo de depósito elegida de modo de dirigir adecuadamente y regular cuantitativamente la liberación de la sal de bupropion. A este respecto, puesto que la plataforma de soporte es impermeable al agua, el material polimérico del núcleo de depósito en ciertas realizaciones puede hincharse sólo en esa porción del depósito no recubierta con la plataforma.

La plataforma de soporte se puede obtener comprimiendo materiales poliméricos preseleccionados sobre el núcleo

de depósito, sumergiendo el núcleo de depósito en una solución de dichos materiales poliméricos en los disolventes orgánicos normales o pulverizando dichas soluciones. Los materiales poliméricos que se pueden usar para preparar la plataforma de soporte se pueden elegir de la clase que comprende acrilatos, celulosas y derivados como etilcelulosa, acetato-propionato de celulosa, polietilenos y metacrilatos y copolímeros del ácido acrílico, alcoholes polivinílicos, etc. Esta plataforma puede tener un espesor de 2 mm si se aplica por compresión y de 10 micras si se aplica por pulverización o inmersión y comprende de 10 % a 90 % de la superficie total del sistema.

Un factor para el control de la liberación de la sal de bupropion es la intensidad y la duración de la fuerza de hinchamiento desarrollada por los materiales poliméricos hinchables contenidos en el núcleo de depósito en contacto con líquidos acuosos. A este respecto, la energía para activar, ejecutar y regular la liberación de la sal de bupropion se puede determinar mediante la fuerza de hinchamiento desarrollada en el núcleo de depósito cuando éste entra en contacto con agua o con líquidos biológicos. Dicha fuerza tiene una intensidad y duración que puede variar en relación con el tipo y la cantidad de los materiales poliméricos usados para formular el depósito y está entre los límites que tienen un valor máximo que se produce en el caso de un depósito que contiene principalmente el polímero hinchable y un valor mínimo que se produce en el caso de un depósito que contiene principalmente el polímero gelificable. Dicho polímero hinchable puede estar presente en una cantidad entre 5 % y 80 % en peso, y dicho polímero gelificable en una cantidad entre 10 % y 90 % en peso, en con respecto a la mezcla que forma el núcleo de depósito.

Un factor de control adicional es la geometría de la plataforma de soporte, que limita el hinchamiento del depósito y dirige la emisión de material desde él. Dentro del alcance de estas realizaciones es posible concebir muchos sistemas para la liberación controlada de la sal de bupropion, que basan su operación en la fuerza de hinchamiento y difieren entre sí por el tipo de plataforma de soporte usada.

En al menos otra realización de la invención diseñada para lograr liberación de orden cero de la sal de bupropion, la cinética de liberación del fármaco desde una matriz de liberación controlada es regida por una combinación de polímeros diferentes con características de hinchamiento diferentes. Más específicamente, primero la sal de bupropion se granula con o se encapsula en un polímero menos hinchable, como una goma, a formar un gránulo. Este gránulo se coloca en una matriz de un polímero erosionable más hinchable. El polímero erosionable más hinchable tiene un coeficiente de velocidad de difusión que es mayor que el coeficiente de velocidad de difusión del polímero relativamente menos hinchable. Promediada durante todo el período de liberación del fármaco, la velocidad de difusión para el polímero más hinchable es mayor que la velocidad de difusión para el polímero menos hinchable. Es esta diferencia general en las velocidades de difusión entre el primer y segundo polímero la que controla la velocidad de liberación del fármaco y le permite al sistema acercarse a una adminstración del fármaco de orden cero durante el período de liberación del fármaco. En al menos una realización, la pectina y la HPMC están presentes como los polímeros más hinchables en relaciones de 2:7 a 4:5 y la gelatina está presente como el polímero menos hinchable.

En al menos otra realización de la invención se proporciona una composición de la matriz de liberación controlada que comprende bromhidrato de bupropion incorporado dentro de una matriz homogénea que incluye cantidades eficaces de al menos dos polímeros que tienen características de humectabilidad opuestas, donde al menos se selecciona un polímero que demuestra una tendencia más fuerte hacia la hidrofobicidad y se seleccionan el o los otros polímeros que demuestran una tendencia más fuerte hacia la hidrofilicidad. En al menos una realización el polímero que demuestra una tendencia más fuerte hacia la hidrofobicidad es etilcelulosa (EC) en tanto que el polímero que demuestra una tendencia más fuerte hacia la hidrofilicidad es hidroxietilcelulosa (HEC) y/o hidroxipropilmetilcelulosa (HPMC). La composición y el dispositivo de la presente invención se

pueden proporcionar como una matriz y se pueden recubrir opcionalmente con un material de recubrimiento que evita el efecto de evacuación gástrica rápida y/o el efecto por el consumo de alimentos asociados con medicamentos ingeridos por vía oral e imparte las características de "furtividad" gastrointestinasles. De conformidad con al menos una realización es un método para preparar un dispositivo para la liberación controlada de la sal de bupropion, donde el método comprende mezclar el bromhidrato de bupropion con 5 % a 25 % en peso del polímero hidrófilo y 1 % a 25 % en peso del polímero hidrófobo, agregando excipientes farmacéuticos adecuados, agentes activos de superficie y lubricantes, granulando la mezcla con disolventes como el alcohol isopropílico, secando la mezcla granular, moliendo la mezcla seca, agregando de 5 % a 70 % en peso de etilcelulosa, agregando un lubricante y opcionalmente un deslizante y comprimiendo los gránulos en forma de matrices. Las matrices se revisten opcionalmente con un revestimiento gastrointestinal o una película de recubrimiento farmacéuticamente aceptable.

En otra realización de la presente invención, se proporciona una forma farmacéutica de matriz hinchable en la cual la sal de bupropion se dispersa en una matriz polimérica que es hinchable con agua en vez de solamente hidrófila, que tiene una velocidad de erosión que es sustancialmente más lenta que su velocidad de hinchamiento y que libera la sal de bupropion principalmente por difusión. La velocidad de difusión de la sal de bupropion fuera de la matriz hinchable se puede enlentecer aumentando el tamaño de la partícula de fármaco, mediante la elección del polímero usado en la matriz, y/o mediante la elección del peso molecular del polímero. La matriz hinchable está compuesta de un polímero de peso molecular relativamente alto que se hincha con la ingestión. En al menos una realización la matriz hinchable aumenta con la ingestión hasta un tamaño que es al menos dos veces su volumen sin hincharse, y eso promueve la retención gástrica durante la modalidad con alimentos. Al hincharse, la matriz hinchable también se puede convertir durante un período prolongado de un polímero vítreo en un polímero que es gomoso en consistencia, o de un polímero cristalino a uno gomoso.

El líquido penetrante causa después la liberación de la sal de bupropion de manera gradual y prolongada mediante el proceso de difusión de la solución, es decir, la disolución de la sal de bupropion en el líquido penetrante y la difusión de la sal de bupropion disuelta fuera de la matriz hinchable. La matriz hinchable en sí es sólida antes de la administración y, una vez administrada, permanece sin disolverse en (es decir, no es erosionada por) el líquido gástrico durante un período suficiente para permitirle a la mayor parte de la sal de bupropion ser liberada por el proceso de difusión de la solución durante la modalidad con alimentos. El factor que limita la velocidad en la liberación de la sal de bupropion de la matriz hinchable es por consiguiente la difusión controlada de la sal de bupropion de la matriz hinchable en lugar de la erosión, la disolución o la descomposición química de la matriz hinchable.

Como tal, el hinchamiento de la matriz polimérica puede lograr al menos los siguientes objetivos: (i) torna la matriz suficientemente grande para provocar retención en el estómago durante la modalidad alimentado; (ii) localiza la liberación del fármaco en el estómago y el intestino delgado de modo que el fármaco tendrá su efecto total sin degradación colónica, inactivación, o pérdida de la biodisponibilidad; (iii) retrasa la velocidad de difusión del fármaco el tiempo suficiente para proporcionar la administración multihora, controlada del fármaco en el estómago.

La sal de bupropion en la matriz hinchable puede estar presente en una cantidad eficaz entre 0,1 % y 99 % en peso de la matriz. Por ejemplo, en ciertas realizaciones el bromhidrato de bupropion está presente en la matriz hinchable en una cantidad entre 0,1 % y 90 %, en otras realizaciones entre 5 % y 90 %, y aún en otras realizaciones entre 10 % y 80 % y en todavía otras realizaciones entre 25 % y 80 % en peso de la matriz hinchable.

El polímero hinchable en agua que forma la matriz hinchable de conformidad con estas realizaciones de la presente invención puede ser cualquier polímero atóxico, que se hinche de una manera dimensionalmente irrestricta

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al embeberse en agua y que asegure una liberación modificada de la sal de bupropion. Los ejemplos no limitantes de los polímeros adecuados para usar en la matriz hinchable incluyen polímeros de celulosa y sus derivados (como por ejemplo; hidroxietilcelulosa, hidroxipropilcelulosa, carboximetilcelulosa y celulosa microcristalina, polisacáridos y sus derivados, óxidos de polialquileno, polietilenglicoles, quitosana, poli(alcohol vinílico), goma xantano, copolímeros del anhídrido maleico, poli(vinilpirrolidona), almidón y polímeros a base de almidón, poli(2-etil-2-oxazolina), poli(etilenimina), hidrogeles de poliuretano y ácidos poliacrílicos reticulados y sus derivados y sus mezclas. Otros ejemplos incluyen copolímeros de los polímeros mencionados en la oración anterior, incluidos copolímeros en bloque y polímeros injertados. Ejemplos específicos de copolímeros incluyen PLURONIC® y TECTONIC®, que son copolímeros en bloque de óxido de polietileno-óxido de polipropileno comercializados por BASF Corporation, Chemicals Div., Wyandotte, Mich., EE.UU.

Los términos "celulosa" y "celulósico", como se usan en esta sección con respecto a las realizaciones de matriz hinchable de la presente invención, pueden denotar un polímero lineal de anhidroglucosa. Los ejemplos no limitantes de los polímeros celulósicos incluyen polímeros celulósicos alquil sustituidos que se disuelven en último término en el tubo digestivo (GI) de una manera predeciblemente retardada. En ciertas realizaciones los derivados de celulosa alquil sustituidos son los sustituidos con grupos alquilo de 1 a 3 átomos de carbono cada uno. Los ejemplos no limitantes incluyen metilcelulosa, hidroximetilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa y sus mezclas. En cuanto a sus viscosidades, una clase de celulosas alquil sustituidas incluye aquellas cuya viscosidad está dentro del rango de 100 a 110.000 centipoise como una solución acuosa al 2 % a 20°C. Otra clase incluye aquellas cuya viscosidad está dentro del rango 1.000 a 4.000 centipoise como una solución acuosa al 1 % a 20°C. En ciertas realizaciones las celulosas alquil sustituidas son hidroxietilcelulosa e hidroxipropilmetilcelulosa. En al menos una realización la hidroxietilcelulosa es NATRASOL® 250HX NF (National

Formulary), comercializada por Aqualon Company, Wilmington, Del., EE.UU.

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 polímeros de celulosa alquil sustituidos. En al menos una realización el óxido de polialquileno es poli(óxido de etileno), término que se usa aquí para denotar un polímero lineal de óxido de etileno sin sustituir. En al menos una realización los polímeros de poli(óxido de etileno) tienen pesos moleculares de 4.000.000 y mayores. Por ejemplo, en cierta realización los polímeros de poli(óxido de etileno) tienen pesos moleculares dentro del rango de 4.500.000 a 10.000.000 y en otras realizaciones tienen pesos moleculares dentro del rango de 5.000.000 a 8.000.000. En ciertas realizaciones los poli(óxido de etileno) son los que tienen un peso molecular promedio dentro del rango de 1 x 105 a 1 x 107, y en otras realizaciones dentro del rango de 9 x 105 a 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 50 a 2.000.000 centipoise para una solución acuosa al 2 % a 20°C. En al menos una realización el poli(óxido de etileno) es uno o más de los POLYOX® NF, grado WSR Coagulante, peso molecular 5 millones y grado WSR 303, peso molecular 7 millones, ambos productos de Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn. EE.UU. Sus mezclas son factibles.

Las gomas de polisacárido, tanto naturales como modificadas (semisintéticas) se pueden usar en las realizaciones de matriz hinchable de la presente invención. Los ejemplos no limitantes incluyen dextrano, goma xantano, goma gelano, goma welano, goma rhamsano y sus mezclas. En al menos una realización la goma de polisacárido es goma xantano.

Los ácidos poliacrílicos reticulados que se pueden usar en las matrices hinchables de la presente invención incluyen aquellos cuyas propiedades son las mismas que las descritas antes para la celulosa alquil sustituida y

los polímeros de óxido de polialquileno. En ciertas realizaciones los ácidos poliacrílicos reticulados son los que tienen una viscosidad que varía de 4.000 a 40.000 centipoise para una solución acuosa al 1 % a 25°C. Los ejemplos no limitantes de los ácidos poliacrílicos reticulados adecuados incluyen CARBOPOL® NF grados 971P, 974P y 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, EE.UU.). Otros ejemplos de ácidos poliacrílicos reticulados adecuados incluyen polímeros conocidos como WATER LOCK®, que son copolímeros de almidón/acrilatos/acrilamida comercializados por Grain Processing Corporation, Muscatine, Iowa, EE.UU.

La hidrofilicidad e hinchabilidad en agua de estos polímeros pueden hacer que las matrices hinchables que contienen fármaco aumenten de tamaño en la cavidad gástrica debido al ingreso de agua para lograr un tamaño que se pueda retener en el estómago cuando se introduzcan durante la modalidad con alimentos. Estas cualidades también hacen que las matrices hinchables se tornen resbaladizas, lo que proporciona resistencia al peristaltismo y además promueve su retención en el estómago. La velocidad de liberación del fármaco de la matriz hinchable depende principalmente de la velocidad de imbibición en agua y la velocidad a la cual el fármaco se disuelve y se difunde del polímero hinchado, que a su vez está relacionada con la concentración de fármaco en la matriz hinchable. Además, debido a que estos polímeros se disuelven muy lentamente en el líquido gástrico, la matriz hinchable mantiene su integridad física durante al menos un período considerable, por ejemplo en muchos casos durante al menos 90 % y preferentemente durante el 100 % del período de dosificación. Después las partículas se disolverán lentamente o se descompondrán. La disolución o descomposición total puede no ocurrir hasta 24 horas o más después que cesa el período de dosificación concebido, aunque en la mayoría de los casos, la disolución o la descomposición total ocurrirá en las 10 a 24 horas siguientes al período de dosificación.

La cantidad de polímero en relación con el fármaco puede variar, dependiendo de la velocidad de liberación del fármaco deseada y del polímero, su peso molecular y los

excipientes que pueden estar presentes en la formulación. La cantidad de polímero será generalmente suficiente para retener al menos 40 % del fármaco dentro de la matriz hinchable una hora después de la ingestión (o inmersión en el líquido gástrico). En ciertas realizaciones, la cantidad de polímero es tal que al menos 50 % del fármaco permanece en la matriz una hora después de la ingestión; en otras realizaciones al menos 60 %, y aún en otras realizaciones al menos 80 %, del fármaco permanece en la matriz hinchable una hora después de la ingestión. En ciertas realizaciones el fármaco será liberado casi completamente de la matriz hinchable en el transcurso de diez horas; y en otras realizaciones en el transcurso de ocho horas, después que la ingestión y la matriz polimérica permanecerá prácticamente intacta hasta que todo el fármaco se libera. En otras realizaciones la cantidad de polímero será tal que después que 2 horas se libera no más de 40 %; después de 4 horas se libera de 40 % a 75 %; después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %. El término "prácticamente intacta" se usa aquí para indicar una matriz polimérica en la cual la porción de polímero conserva prácticamente su tamaño y forma sin deterioro debido a que se solubiliza en el líquido gástrico o debido a que se rompe en fragmentos o partículas pequeñas.

En otras realizaciones de ejemplo la matriz hinchable liberará después de 2 horas no más de 40 % de bupropion HBr, después de 4 horas de 40 % a 75 %, después de 8 horas al menos 75 % y después que 16 horas al menos 85 %.

Los polímeros hinchables en agua de las matrices hinchables se pueden usar individualmente o en combinación. Ciertas combinaciones proporcionarán a menudo una liberación más controlada del fármaco que sus componentes cuando se usan individualmente. Los ejemplos incluyen polímeros 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 esta invención se pueden lograr en una gama amplia de concentraciones del fármaco y niveles de

polímero, con la relación de pesos entre fármaco y polímero variando en general de 0,01:99,99 a 80:20. Por ejemplo, en ciertas realizaciones las concentraciones del fármaco (expresadas en términos de porcentaje de peso del fármaco en relación con el total de fármaco y polímero) están dentro del rango de 15 % a 80 %; en otras realizaciones dentro del rango de 30 % a 80 %; y aún en otras realizaciones dentro del rango de 30 % a 70 %. En al menos una realización la concentración de fármaco está dentro del rango de 0,01 % a 80 %, y en al menos otra realización de 15 % a 80 %. En al menos una realización la relación de pesos entre bromhidrato de bupropion y polímero en la matriz hinchable es de 15:85 a 80:20.

Las formulaciones de las matrices hinchables de la presente invención pueden adquirir la forma de micropartículas, comprimidos o micropartículas retenidas en cápsulas. En al menos una realización la formulación comprende micropartículas consolidadas en una masa compactada para la ingestión, aunque la masa compactada se separará en partículas individuales después de la ingestión. Se pueden usar los métodos convencionales para consolidar las micropartículas de esta manera. Por ejemplo, las micropartículas se pueden colocar en cápsulas de gelatina conocidas en el área como cápsulas "rellenas duras" y cápsulas "blandas elásticas". Las composiciones de estas cápsulas y los procedimientos para llenarlas son conocidos por los técnicos con experiencia en la formulación de fármacos y su fabricación. El material de encapsulado debe ser muy soluble para que las partículas se liberen y se dispersen rápidamente en el estómago después de la ingestión de la cápsula.

En ciertas realizaciones de las matrices hinchables de la presente invención, la formulación contiene una cantidad adicional de sal de bupropion u otro fármaco aplicada como un recubrimiento que se disuelve rápidamente en la parte exterior de la micropartícula o el comprimido. Este recubrimiento se denomina "dosis inicial" y se incluye para la liberación inmediata en la circulación sanguínea del receptor después de la ingestión de la formulación sin experimentar primero el proceso de difusión por el que el resto del fármaco de la formulación debe pasar antes de ser liberado. La "dosis inicial" puede ser lo

suficientemente alta para elevar rápidamente la concentración sanguínea de la droga pero no lo bastante alta como para producir la sobredosis transitoria que es característica de formas farmacéuticas de liberación inmediata que no están formuladas de conformidad con esta invención.

En al menos una realización de las matrices hinchables de la presente invención, la forma farmacéutica es una cápsula de gelatina de tamaño 0 que contiene o dos o tres pelets de polímero impregnado de fármaco. Para las cápsulas de dos pelets, los pelets tienen forma cilíndrica, de 6,6 ó 6,7 mm (o más generalmente, 6,5 a 7 mm) de diámetro y 9,5 ó 10,25 mm (o más generalmente, 9 a 12 mm) de longitud. Para las cápsulas de tres pelets, los pelets tienen nuevamente forma cilíndrica, 6,6 mm de diámetro y 7 mm de longitud. Para una cápsula de gelatina de tamaño 00 con dos pelets, los pelets son cilíndricos, de 7,5 mm de diámetro y 11,25 mm de longitud. Para una cápsula de gelatina de tamaño 00 con tres pelets, los pelets son cilíndricos, de 7,5 mm de diámetro y 7,5 mm de longitud. En al menos otra realización, la forma farmacéutica es un único comprimido, alargado, con dimensiones de 18 a 22 mm de longitud, 6,5 a 10 mm de ancho y 5 a 7,5 mm de altura. En al menos otra realización, la forma farmacéutica es un único comprimido, alargado, con dimensiones de 18 a 22 mm de longitud, 6,5 a 7,8 mm de ancho y 6,2 a 7,5 mm de altura. En al menos una realización las dimensiones son 20 mm de longitud, 6,7 mm de ancho y 6,4 mm de altura. Éstos son sólo ejemplos; las formas y los tamaños se pueden variar considerablemente.

La mezcla particulada fármaco/polímero o la matriz de polímero hinchable impregnada de fármaco se pueden preparar mediante diversas técnicas convencionales de mezcla, trituración y fabricación fácilmente evidentes para los técnicos capacitados en la química de las formulaciones de fármacos. Los ejemplos de tales técnicas 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

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automática Elizabeth-Hata single-sided Hata Auto Press, con 15, 18 ó 22 estaciones y que se puede adquirir a Elizabeth-Hata Internacional, Inc., North Huntington, Pa., EE.UU.; (2) Inyección 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 de compresión; y (4) Extrusión en forma de una pasta, en un molde o de un extrudado para cortar en trozos.

En cuanto a las matrices hinchables de la presente invención, cuando las micropartículas se elaboran mediante compresión directa, la adición de lubricantes puede ser útil y a veces importante para promover el flujo del polvo y para evitar el decapado de la micropartícula (ruptura de una porción de la partícula) cuando se reduce la presión. Los ejemplos no limitantes de los lubricantes adecuados incluyen estearato de magnesio (en una concentración entre 0,25 % y 3 % en peso y en ciertas realizaciones en menos de 1 % en peso, en la mezcla de polvo), y aceite vegetal hidrogenado (en ciertas realizaciones triglicéridos hidrogenados y refinados de los ácidos esteárico y palmítico en 1 % a 5 % en peso, por ejemplo en al menos una realización en 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 utilidad cuando se las administra a un sujeto que está en el estado digestivo (también 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 retención gástrica o de tránsito gástrico del contenido del estómago.

Las matrices de liberación controlada de la presente invención se pueden preparar mediante métodos conocidos en el área como los descritos en las patentes indicadas más arriba (por ejemplo, Patente de los EE.UU. 5,965,161). Un ejemplo de un método de fabricación de

matrices de liberación controlada es la extrusión por fusión de una mezcla que contiene la sal de bupropion, el o los polímeros hidrófobos, el o los polímeros hidrófilos y opcionalmente un aglutinante, un plastificante y otros excipientes como los descritos precedentemente. Otros ejemplos de métodos de fabricación de matrices de liberación controlada incluyen granulación húmeda, granulación seca (por ejemplo, aglutinación, compactación con rodillos), compresión directa, granulación por fusión y granulación rotatoria.

Además, las partículas de liberación controlada que se pueden comprimir o colocar en las cápsulas se pueden producir combinando la sal de bupropion y un 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 orgánico o inorgánico insoluble. Los ejemplos de los posibles componentes fundibles hidrófobos incluyen materiales hidrófobos como ceras o aceites naturales o sintéticos (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 fusión de 35°C a 140°C. Los ejemplos de agentes que modifican la liberación incluyen polietilenglicol y materiales particulados como fosfato dicálcico y lactosa.

En ciertas realizaciones, las matrices de liberación controlada se pueden producir trabajando mecánicamente una mezcla de una sal de bupropion, un componente fundible hidrófobo, y opcionalmente un componente de liberación incluido un material fundible soluble en agua o un material particulado orgánico o inorgánico soluble o insoluble en condiciones de mezcla que produzca aglomerados, rompiendo los aglomerados para producir iniciadores de la liberación controlada que tengan las propiedades de liberación deseadas; y opcionalmente agregando más vehículo o diluyente y repitiendo los pasos de mezcla hasta que se obtengan los iniciadores de la liberación controlada con propiedades de liberación deseadas. Estas partículas también se pueden separar por

tamaño (por ejemplo, tamizando y encapsulando en cápsulas o comprimiendo en forma de matriz).

La cantidad de material fundible hidrófobo usado en los métodos mencionados antes puede variar de 10 % a 90 % en peso. Los mezcladores útiles en dichos métodos 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 40°C o mayor y la mezcla logra una textura granular cohesiva que comprende los tamaños deseados de partícula.

Según se observa si la mezcla contiene aglomerados, éstos se pueden romper usando métodos convencionales para producir una mezcla de polvo y partículas del tamaño deseado que, se pueden separar por tamaño usando un cedazo, tamiz o malla del tamaño apropiado. Este material puede ser devuelto a un mezclador de gran velocidad y procesado aún más según se desee hasta que los materiales fundibles hidrófobos empiecen a ablandarse/fundirse y opcionalmente se puede agregar más material hidrófobo seguir mezclando hasta que se obtengan partículas con el rango de tamaño deseado. Aún más, las partículas que contienen sal de bupropion se pueden producir mediante el proceso de fusión conocido en el área y combinar en cápsulas o comprimir en forma de matrices.

Estas partículas se pueden combinar con uno o más excipientes como diluyentes, lubricantes, aglutinantes, auxiliares de flujo, desintegrantes, agentes que actúan en la superficie, materiales solubles en agua, colorantes y similares.

Además, las matrices de liberación controlada se pueden recubrir opcionalmente con uno o más recubrimientos funcionales o no funcionales usando métodos de recubrimiento conocidos. Los ejemplos de recubrimientos pueden incluir el recubrimiento de control de la liberación XL y el recubrimiento de matriz EA descritos aquí, que pueden controlar además la liberación de la sal de bupropion y/o de otro fármaco.

En al menos una realización, las matrices de liberación controlada pueden recubrirse cada una con al menos un recubrimiento que enmascara el sabor. El recubrimiento que enmascara el sabor puede enmascarar el sabor de la sal de bupropion en las matrices. En al menos una realización las formulaciones de recubrimiento que enmascaran el sabor contienen ingredientes poliméricos. Se contempla que se pueden usar en el recubrimiento que enmascara el sabor otros excipientes compatibles con los objetivos de la presente invención.

En al menos una realización de la forma farmacéutica de matriz, el recubrimiento que enmascara el sabor comprende un polímero como etilcelulosa, que se puede usar como un polímero seco (como Ethocel®, Dow Corning) solubilizado en el disolvente orgánico antes de usar, o como una dispersión acuosa. Una dispersión acuosa comercialmente disponible de etilcelulosa es Aquacoat® (FMC Corp., Filadelfia, Pa., EE.UU.). El Aquacoat® se puede preparar disolviendo la etilcelulosa en un disolvente orgánico inmiscible con agua y luego emulsionar el mismo en agua en presencia de un tensioactivo y un estabilizador. Después de la homogeneización para generar gotitas submicrónicas, el disolvente orgánico se evapora al vacío para formar un pseudolátex. El plastificante no se incorpora en el pseudolátex durante la fase de fabricación. Por lo tanto, antes de usar el mismo como un recubrimiento, el Aquacoat se mezcla íntimamente con un plastificante adecuado antes de usar. Otra dispersión acuosa de etilcelulosa está comercialmente disponible como Surelease® (Colorcon, Inc., West Point, Pa., EE.UU.). Este producto se puede preparar incorporando un plastificante en la dispersión durante el proceso de fabricación. Se prepara una masa fundida caliente de un polímero, un plastificante (por ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, ácido oleico) como una mezcla homogénea, que luego se diluye con una solución alcalina para obtener una dispersión acuosa que se puede aplicar directamente sobre los sustratos.

En otras realizaciones de la forma farmacéutica de matriz, se pueden emplear polímeros polimetacrilato acrílicos como polímeros enmascaradores del sabor. En al menos una realización, el recubrimiento que enmascara el

sabor es una laca de resina acrílica usada en forma de una dispersión acuosa, como las que se obtienen comercialmente de Rohm Pharma con el nombre comercial Eudragit® o de BASF con el nombre comercial Kollicoat®. En otras realizaciones preferidas, el recubrimiento acrílico comprende una mezcla de dos lacas de resina acrílicas comercializadas por Rohm Pharma con el nombre comercial Eudragit® RL y Eudragit® RS, respectivamente. Eudragit® RL y Eudragit® RS son copolímeros de ésteres acrílicos y metacrílicos con un contenido bajo de grupos amonio cuaternario, la relación molar entre los grupos amonio y los restantes ésteres (met)acrílicos neutros es de 1:20 en Eudragit® RL y 1:40 en Eudragit® RS. El peso molecular medio es 150.000. Las designaciones del código RL (permeabilidad alta) y RS (permeabilidad baja) se refieren a las propiedades de permeabilidad de estos agentes. Las mezclas Eudragit® RL/RS son insolubles en agua y en los líquidos digestivos. Sin embargo, los recubrimientos elaborados a partir de ellos son hinchables y permeables en soluciones acuosas y líquidos digestivos. Las dispersiones o soluciones Eudragit® RL/RS de la presente invención se pueden mezclar en cualquier proporción deseada para obtener en último término un recubrimiento que enmascara el sabor con un perfil de disolución del fármaco deseable. Se pueden obtener formulaciones de liberación controlada deseables, por ejemplo, a partir de un recubrimiento retardador derivado de 100 % de Eudragit® RL; 50 % de Eudragit® RL con 50 % de Eudragit® RS; y 10 % de Eudragit® RL con 90 % de Eudragit® RS.

En otras realizaciones de la forma farmacéutica de matriz, el polímero que enmascara el sabor puede ser un polímero acrílico de carácter catiónico a base de metacrilato de dimetilaminoetilo y ésteres del ácido metacrílico neutros (como Eudragit® E, comercializado por Rohm Pharma). Los recubrimientos de polímero acrílico hidrofóbo de la presente invención pueden incluir además un copolímero neutro a base de poli(met)acrilatos, como Eudragit® NE (NE = éster neutro), comercializado por Rohm Pharma. Las películas de laca de Eudragit® NE 30D son insolubles en agua y líquidos digestivos, pero permeables e hinchables.

En otras realizaciones de la forma farmacéutica de matriz, el polímero que enmascara el sabor es una dispersión de poli(acrilato de etilo, metacrilato de metilo) 2:1 (Kollicoat® EMM 30 D, BASF).

En otras realizaciones de la forma farmacéutica de matriz, el polímero que enmascara el sabor puede ser un acetato de polivilo estabilizado con polivinilpirrolidona y lauril sulfato de sodio como Kollicoat® SR30D (BASF).

Otros polímeros que enmascaran el sabor usados en las formas farmacéuticas de matriz incluyen hidroxipropilcelulosa (HPC); hidroxipropilmetilcelulosa (HPMC); hidroxietilcelulosa; gelatina; gelatina/acacia; gelatina/acacia/vinilmetiléter-anhídrido maleico; gelatina/acacia/anhídrido etilenmaleico; carboximetilcelulosa; alcohol polivinílico; nitrocelulosa; copolímeros injertados de alcohol polivinílico-polietilenglicol; laca; cera y sus mezclas.

Los recubrimientos que enmascaran el sabor se pueden aplicar a las matrices a partir de una o más soluciones o suspensiones de disolventes orgánicos o acuosos. En al menos una realización de las formas farmacéuticas de matriz los disolventes orgánicos que se pueden usar para aplicar los recubrimientos que enmascaran el sabor incluyen uno o más entre acetona, alcoholes inferiores como etanol, isopropanol y mezclas de alcohol/agua, hidrocarburos clorados y similares. Los dispositivos empledos para recubrir las matrices de la invención con un recubrimiento que enmascara el sabor incluyen los utilizados convencionalmente en el procesamiento farmacéutico, como los dispositivos de recubrimiento de lecho fluidizado. Los recubrimientos con control de la liberación aplicados a las matrices pueden contener ingredientes diferentes de los polímeros celulósicos. También se pueden usar uno o más colorantes, aromatizantes y edulcorantes en el recubrimiento que enmascara el sabor.

En algunas realizaciones de las formas farmacéuticas de matriz se puede incluir un formador de poros en el recubrimiento que enmascara el 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 el recubrimiento que enmascara el sabor. Los formadores de poros pueden ser inorgánicos u orgánicos y pueden ser de naturaleza particulada e incluir materiales que se pueden disolver, extraer o lixiviar del recubrimiento en el ambiente de uso. Después de la exposición a líquidos en el ambiente de uso, los formadores de poros se pueden, por ejemplo, disolver y se forman canales y poros que se llenan con el líquido ambiental.

Por ejemplo, los formadores de poros de ciertas realizaciones de las formas farmacéuticas de matriz pueden comprender uno o más polímeros hidrófilos solubles en agua para modificar las características de liberación de la formulación. Los ejemplos de los polímeros hidrófilos adecuados usados como formadores de poros incluyen hidroxipropilmetilcelulosa, éteres de celulosa y derivados proteicos de estos polímeros, los éteres de celulosa, especialmente hidroxialquilcelulosas y carboxialquilcelulosas. Asimismo, se pueden usar polímeros solubles en agua sintéticos, cuyos ejemplos incluyen polivinilpirrolidona, polivinilipirrolidona reticulada, óxido de polietileno, polidextrosa soluble en agua, sacáridos y polisacáridos, como pullulan, dextrano, sacarosa, glucosa, fructosa, manitol, lactosa, manosa, galactosa y sorbitol. En al menos una realización, el polímero hidrófilo comprende hidroxipropilmetilcelulosa.

Otros ejemplos no limitantes de formadores de poros 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 y citrato de sodio. Los sólidos que forman poros también pueden ser polímeros que son solubles en el ambiente de uso, como los Carbowax y Carbopol. Además, los formadores de poros abarcan dioles, polioles, alcoholes polihídricos, polialquilenglicoles, poliglicoles y poli(a-w)alquilendioles. Otros formadores de poros que pueden ser útiles en las formulaciones de la presente invención incluyen almidón, almidón modificado y derivados del almidón, gomas, incluidas, pero no exclusivamente, goma xantano, ácido algínico, otros alginatos, bentonita, veegum (silicato de aluminio y

magnesio), agar, goma guar, goma de algarrobo, goma arábiga, quince psyllium, semilla de lino, goma de quimbombó, arabinogalactano, pectina, goma tragacanto, escleroglucano, dextrano, amilosa, amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de intercambio iónico, como polimetacrilato de potasio, carragenina, carragenina kappa, carragenina lambda, goma karaya, goma biosintética, etc. Otros formadores de poros incluyen materiales útiles para hacer láminas microporosas en los ambientes de uso, como policarbonatos compuestos de poliésteres lineales del ácido carbónico en los que los grupos carbonato reaparecen en la cadena polimérica, materiales microporosos como bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas, copolímeros modacrílicos microporosos, estireno-acrílico microporoso y sus copolímeros, polisulfonas porosas, poli(vinilideno) halogenado, policloroéteres, polímeros de acetal, poliésteres preparados por esterificación de un ácido dicarboxílico o anhídrido con un alquilenpoliol, poli(sulfuros de alquileno), fenólicos, poliésteres, polímeros porosos asimétricos, polímeros olefínicos reticulados, homopolímeros hidrófilos microporosos, copolímeros o interpolímeros con una menor densidad aparente y otros materiales similares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas), poli(benzimidazoles), colodión, proteínas regeneradas, poli(vinilpirrolidona) reticulada semisólida y sus mezclas.

En general, la cantidad de formador de poros incluida en los recubrimientos que enmascaran el sabor de ciertas realizaciones de las formas farmacéuticas de matriz pueden ser de 0,1 % a 80 %, en peso, en relación con el peso combinado de polímero y formador de poros. El porcentaje de formador de poros como se relaciona con el peso seco del polímero que enmascara el sabor, puede tener una influencia sobre las propiedades de liberación del fármaco desde la matriz recubierta. En al menos una realización que usa formadores de poros solubles en agua como hidroxipropilmetilcelulosa, puede haber presente una relación de peso seco polímero que enmascara el sabor:formador de poros entre 10:1 y 1:1. En ciertas realizaciones la relación de pesos secos polímero que

enmascara el sabor:formador de poros es de 8:1 a 1,5:1; y en otras realizaciones de 6:1 a 2:1. En al menos una realización que usa Eudragit® NE30D como polímero que enmascara el sabor y una hidroxipropilmetilcelulosa (viscosidad aprox. 5 cp (en una solución acuosa al 2 %)) como Methocel® E5, Pharmacoat 606G como el formador de poros soluble en agua, está presente una relación de pesos secos polímero que enmascara el sabor:formador de poros de 2:1.

Los colorantes que se pueden usar en el recubrimiento que enmascara el sabor de ciertas realizaciones de las formas farmacéuticas de matriz incluyen los colorantes (FD&C) de alimentos, fármacos y cosméticos, (D&C) de fármacos y cosméticos o los colorantes externos (Ext. D&C) de fármacos y cosméticos. Estos colorantes son tinturas, lacas y ciertos colorantes naturales y derivados. Las lacas útiles incluyen tinturas absorbidas sobre hidróxido de aluminio u otros vehículos adecuados.

Los saborizantes que se pueden usar en el recubrimiento que enmascara el sabor de ciertas realizaciones de las formas farmacéuticas de matriz incluyen líquidos saborizantes naturales y sintéticos. Una lista ilustrativa de dichos saborizantes incluye aceites volátiles, aceites saborizantes sintéticos, compuestos aromáticos saborizantes, aceites, líquidos, oleorresinas y extractos derivados de plantas, hojas, flores, frutos, tallos y sus combinaciones. Una lista representativa, no limitante, de éstos incluye aceites cítricos, como de limón, naranja, toronja, lima y pomelo y esencias de frutas, incluidas manzana, pera, durazno, uva, frutilla, frambuesa, cereza, ciruela, ananás, albaricoque u otros saborizantes de fruta. Otros saborizantes útiles incluyen aldehídos y ésteres, como benzaldehído (cereza, almendra); citral, es decir, alfa citral (limón, lima); neral, es decir, beta citral (limón, lima); decanal (naranja, limón); aldehído C-8 (cítricos); aldehído C-9 (cítricos); aldehído C-12 (cítricos); tolil aldehído (cereza, almendra); 2,6-dimetiloctanal (fruto verde); 2-dodenal (mandarina); sus mezclas y similares.

Los edulcorantes que se pueden usar en el recubrimiento que enmascara el sabor de ciertas realizaciones de las

formas farmacéuticas de matriz incluyen glucosa (jarabe de maíz), dextrosa, azúcar invertido, fructosa y sus mezclas (cuando no se usan como vehículos); sacarina y sus diversas sales, como la sal de sodio; dipéptidos edulcorantes como aspartamo; compuestos dihidrochalcona, glicirricina; Steva Rebaudiana (estevióside); derivados clorados de sacarosa como sucralosa; y alcoholes de azúcares como sorbitol, manitol, xilitol y similares. También se contemplan hidrolisados de almidón hidrogenado y edulcorantes sintéticos como 3,6-dihidro-6-metil-1-1-1,2,3-oxatiazin-4-1-2,2-dióxido, en particular la sal de potasio (acesulfamo-K) y sus sales de sodio y calcio. Los edulcorantes se pueden usar solos o en cualquier combinación.

El recubrimiento de la matriz que enmascara el sabor también puede incluir uno o más excipientes farmacéuticamente aceptables como lubricantes, emulsionantes, 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 el recubrimiento que enmascara el sabor de la presente invención incluyen, pero no exclusivamente, ácido adípico, 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 fumarato de sodio, aceite mineral ligero, ésteres de ácidos graso como behenato de glicerilo, (es decir Compritol™), Stear-O-Wet™, Myvatex ™TL y sus mezclas. En al menos una realización, el lubricante se selecciona entre estearato de magnesio y talco. Las combinaciones de estos lubricantes son factibles. Cada lubricante puede estar presente en una cantidad entre 1 % y 100 % en peso del peso seco del polímero en el recubrimiento que enmascara el sabor. Por ejemplo, en ciertas realizaciones en las que el polímero que enmascara el sabor es Eudragit® NE30D o Eudragit® NE40D

(Rohm America LLC) junto con un formador de poros hidrófilo, el lubricante está presente en una cantidad entre 1 % y 30 % en peso del peso seco del polímero; en otras realizaciones entre 2 % y 20 %; y aún en otras realizaciones en 10 % en peso del peso seco del recubrimiento de la matriz que enmascara el sabor. En otra realización donde el polímero que enmascara el sabor es etilcelulosa (Ethocel™ polímero PR100, PR45, PR20, PR10 o PR7, o una mezcla), el lubricante puede estar presente en una cantidad entre 10 % y 100 % en peso del peso seco del recubrimiento de la matriz que enmascara el sabor; en otra realización entre 20 % y 80 %; y aún en otras realizaciones en 50 % en peso del peso seco del recubrimiento de la matriz que enmascara el sabor. En otras realizaciones, el recubrimiento que enmascara el sabor no incluye un formador de poros.

Se pueden incluir uno o más emulsionantes (también denominados emulsificantes o emulgentes) en el recubrimiento que enmascara el sabor de la matriz para facilitar la emulsificación real durante la fabricación del recubrimiento y también para asegurar la estabilidad de la emulsión durante la vida útil en depósito del producto. Los emulsionantes útiles para el recubrimiento de la matriz que enmascara el sabor incluyen, pero no exclusivamente, materiales de origen natural y sus derivados semisintéticos, como los polisacáridos, así como ésteres de glicerol, éteres de celulosa, ésteres de sorbitán (por ejemplo, monooleato de sorbitán o Span™ 80) y polisorbatos (por ejemplo, Tween™ 80). Las combinaciones de emulsionantes son factibles. En al menos una realización, el emulsionante es Tween™ 80. El o los emulsionantes pueden estar presentes en una cantidad entre 0,01 % y 5 % en peso del peso seco del polímero que enmascara el sabor de la matriz. Por ejemplo, en ciertas realizaciones el emulsionante está presente en una cantidad entre 0,05 % y 3 %; en otras realizaciones entre 0,08 % y 1,5 %, y aún en otras realizaciones en 0,1 % en peso del peso seco del polímero que enmascara el sabor de la matriz.

Se pueden incluir uno o más antiespumantes en el recubrimiento que enmascara el sabor de la matriz para reducir la producción de burbujas o de espuma durante la

fabricación del recubrimiento. Los antiespumantes útiles para la composición del recubrimiento incluyen, pero no exclusivamente, simeticona, poliglicol, aceite de silicio y sus mezclas. En al menos una realización el antiespumante es Simeticona C. El antiespumante puede estar presente en una cantidad entre 0,1 % y 10 % del peso del recubrimiento que enmascara el sabor de la matriz. Por ejemplo, en ciertas realizaciones el antiespumante está presente en una cantidad entre 0,2 % y 5 %; en otras realizaciones entre 0,3 % y 1 %, y áun en otras realizaciones en 0,6 % en peso del peso seco del polímero que enmascara el sabor de la matriz.

Se pueden incluir uno o más plastificantes en el recubrimiento que enmascara el sabor de la matriz para proporcionar mayor flexibilidad y durabilidad durante la fabricación. Los plastificantes que se pueden usar en el recubrimiento que enmascara el sabor de la matriz incluyen monoglicéridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicérido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de colza, aceite de oliva, aceite de sésamo, citrato de trietilo; alcoholes polihídricos, glicerol, glicerina, sorbitol, ésteres 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 epoxidado, trimelitato de triisoctilo, ftalato de dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, 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, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de glicerol y sus mezclas. El plastificante puede estar presente en una cantidad entre 1 % y 80 % del peso seco del polímero que enmascara el sabor. Por ejemplo, en ciertas realizaciones el plastificante está presente en

una cantidad entre 5 % y 50 %, en otras realizaciones entre 10 % y 40 % y aún en otras realizaciones en 20 % del peso seco del polímero que enmascara el sabor.

El recubrimiento que enmascara el sabor puede estar presente en una cantidad entre 1 % y 90 % en peso de la matriz, dependiendo de la elección del polímero, la relación polímero:formador de poros y el área superficial total de la formulación de la matriz. 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 polímero que enmascara el sabor usada durante la fabricación está relacionada con el área superficial total del lote de matrices sin recubrir que requiere un recubrimiento. Por ejemplo, la cobertura del área superficial del polímero que enmascara el sabor puede variar de 0,5 mg/cm^2 a 20 mg/cm^2. Por ejemplo, en ciertas realizaciones la cobertura del área superficial del polímero que enmascara el sabor es de 0,6 mg/cm^2 a 10 mg/cm^2, y en otras realizaciones es de 1 mg/cm^2 a 5 mg/cm^2. En al menos una realización de la invención, se emplea Eudragit® E como el polímero que enmascara el sabor a una cobertura de área superficial de 4 mg/cm^2.

A falta de una determinación exacta del área superficial total de una matriz, la cantidad de polímero que enmascara el sabor que se debe aplicar se puede expresar como un porcentaje de la matriz sin recubrir. Por ejemplo, en ciertas realizaciones el recubrimiento que enmascara el sabor está presente en una cantidad entre 5 % y 60 %; en otras realizaciones entre 10 % y 40 %; y aún en otras realizaciones entre 15 % y 35 % en peso de la matriz. En al menos una realización el recubrimiento que enmascara el sabor está presente en una cantidad de 30 % en peso de la matriz.

Los ejemplos proféticos de las formulaciones de comprimidos de matriz se describen a continuación. Se debe comprender que estos ejemplos están destinados a ser ejemplares y que los constituyentes específicos, sus cantidades y métodos de formulación se pueden variar para lograr diferentes características de liberación:

En al menos una realización, las matrices controladas comprenden:

Bupropion HBr	30,0 % en peso de la matriz
Hidroxipropilmetilcelulosa E50	10,0 % en peso de la matriz
Hidroxipropilmetilcelulosa K15M	30,0 % en peso de la matriz
Fosfato de calcio deshidratado	9,5 % en peso de la matriz
ATMUL™ 84S (*mono/di/tri glicéridos*)	20,0 % en peso de la matriz
Estearato de magnesio	0,5 % en peso de la matriz

La preparación de la formulación de la matriz puede ser la siguiente: Combinar el fármaco, una porción 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 húmeda. Pasar el material húmedo a través de un tamiz para hacer los gránulos resultantes de tamaño uniforme (para lograr un secado uniforme) y secar en una estufa a 40°C durante 24 horas. Moler los gránulos secos a través de un molino Fitzpatrick, con cuchillas delanteras, y recojer el material en un mezclador. Agregar el estearato de magnesio y mezclar durante 5 minutos. La mezcla resultante se comprime en una compresora de comprimidos adecuada.

En al menos una realización, las matrices de liberación controlada comprenden un núcleo de depósito y una plataforma de soporte. La preparación del núcleo de depósito puede ser la siguiente: Los núcleos de depósito se pueden preparar usando los materiales siguientes en las cantidades establecidas:

Bupropion HBr	45,0 g
Hidroxipropilmetilcelulosa (methocel K 100 M-Colorcon)	35,0 g
manitol	10,0 g

etilcelulosa (alta viscosidad-BDH)	3,75 g
3,75 g estearato de magnesio	1,0 g
5:1 mezcla de etanol-cloroformo	75,0 ml

El bupropion HBr se mezcla íntimamente 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 homogénea resultante se fuerza a través de un tamiz de 800 micras y luego se seca para obtener un granulado que se pasa a través de un tamiz de 420 micras. El granulado homogéneo obtenido se mezcla con el estearato de magnesio y luego se comprime usando punzones cóncavos de 7 mm de diámetro (radio de curvatura de 9 mm) usando una presión de 3.000 kg/cm^2 para obtener núcleos de depósito cilíndricos con bases convexas.

La aplicación de la plataforma de soporte puede ser del modo siguiente: La plataforma de soporte se puede aplicar recubriendo una o ambas bases convexas del núcleo de depósito con una solución de 15 g de copolímero acrílico-metacrílico de baja permeabilidad (Eudragit RS Rohm Pharma) en cloruro de metileno en una cantidad para obtener 100 ml. Posteriormente se aplican 0,3 ml de dicha solución a cada base que se va a recubrir, teniendo cuidado de proteger la superficie lateral del núcleo. Después el sistema se seca con aire tibio. La cantidad de material polimérico 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 OPE que comprende:

Bupropion HBr	50 %
OPE WSR Coagulante (*óxido de polietileno*)	15 %
Methocel K100M (*hidroxipropilmetilcelulosa*)	15 %
Avicel PH101 (*celulosa microcristalina*)	19 %
Estearato de magnesio	1 %

La preparación de la formulación de matriz de comprimido basada en OPE puede ser la siguiente: Los excipientes se mezclan en seco en un mezclador apropiado y se comprimen en forma de comprimidos usando equipos convencionales.

Multiparticulados

Micropartículas

En ciertas realizaciones de la presente invención, se proporciona un sistema multiparticulado que contiene micropartículas múltiples que cada una contiene una cantidad eficaz de una sal de bupropion y al menos un excipiente farmacéuticamente aceptable. En al menos una realización la sal de bupropion es bromhidrato de bupropion. Los multiparticulados pueden estar contenidos dentro de una cápsula, o se pueden comprimir en forma de matriz o comprimido, que al ingerir se disuelven en múltiples unidades (por ejemplo, pelets), donde las subunidades o pelets poseen las propiedades deseadas de liberación controlada de la forma farmacéutica. Los multiparticulados o las formas farmacéuticas múltiples pueden estar rodeados por uno o más recubrimientos. Los ejemplos de dichos recubrimientos incluyen recubrimientos poliméricos de liberación controlada, recubrimientos de liberación retardada, recubrimientos entéricos, recubrimientos de liberación inmediata, recubrimientos que enmascaran el sabor, recubrimientos de liberación extendida y recubrimientos no funcionales.

La sal de bupropion puede estar presente en las micropartículas en una cantidad eficaz entre 0,1 % y 99 % en peso de las micropartículas. Por ejemplo, en ciertas realizaciones el bromhidrato de bupropion está presente en las micropartículas en una cantidad entre 0,1 % y 90 %, en otras realizaciones entre 5 % y 90 %, aún en otras realizaciones entre 10 % y 80 % y todavía en otras realizaciones entre 25 % y 80 % en peso de la micropartícula. En ciertas realizaciones en que las micropartículas se preparan usando un proceso de esferonización, el bromhidrato de bupropion puede estar presente en las micropartículas en una cantidad entre 0,1 % y 60 %; en otras de dichas realizaciones entre 5 % y 50 %; y aún en otras de dichas realizaciones entre 10 % y 40 % en peso de la micropartícula. En al menos una

realización en la que las micropartículas se preparan usando un proceso de esferonización el bromhidrato de bupropion está presente en la micropartícula en una cantidad de 30 % en peso de la micropartícula.

Además de la sal de bupropion, las micropartículas de la presente invención también incluyen al menos un excipiente farmacéuticamente aceptable. Se pueden agregar excipientes para facilitar la preparación, la aceptabilidad por el paciente y la acción de la forma farmacéutica como un sistema de liberación del fármaco. Los excipientes incluyen auxiliares de esferonización, potenciadores de la solubilidad, desintegrantes, diluyentes, lubricantes, aglutinantes, rellenos, deslizantes, agentes de suspensión, emulsionantes, antiespumantes, saborizantes, colorantes, estabilizadores químicos, modificadores del pH, etc. 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, un excipiente puede afectar a las propiedades de una composición de una serie de maneras, y muchos excipientes usados en las composiciones pueden describirse por lo tanto como multifuncionales.

Las micropartículas de la presente invención se pueden fabricar usando las técnicas corrientes conocidas por un técnico con experiencia. Las micropartículas útiles incluyen micropartículas distribuidas en capas de fármaco y micropartículas que contienen fármaco.

Micropartículas que contienen fármaco

Las micropartículas que contienen fármaco en el núcleo se pueden preparar mediante una serie de procedimientos diferentes. Por ejemplo: En un proceso de secado por aspersión, se pulveriza una solución acuosa de material del núcleo y una solución caliente de polímero en el aire caliente, después se evapora el agua y el sólido seco se separa en forma de pelets, por ejemplo por suspensión en aire. Un proceso de secado por aspersión puede producir pelets huecos cuando el líquido se evapora a una velocidad que es mayor que la de la difusión de las sustancias disueltas de vuelta en el interior de la gotita, o si se debe a la acción capilar la sustancia

disuelta migra hacia afuera con el líquido a la superficie de la gotita, dejando detrás un vacío. Otro ejemplo es un proceso de congelación por pulverización, donde una suspensión acuosa espesa del material farmacológico que es insoluble en una masa fundida se congela por pulverización para obtener partículas discretas de los materiales insolubles recubiertos con la sustancia congelada. Otro ejemplo es un proceso de granulación/peletización basado en un lecho fluidizado, donde un fármaco seco se suspende en una corriente de aire caliente para formar un lecho fluidizado constantemente agitado. Una cantidad de líquido aglutinante o de granulación se introduce luego en forma finamente dispersa para causar peletización.

Las micropartículas que contienen fármaco de la presente invención también se pueden hacer mediante, por ejemplo, un proceso de esferonización. Un método de fabricación de micropartículas que contienen fármaco es la tecnología patentada por el solicitante CEFORM™ (Microsferas/Micropartículas Centrífugamente Extruidas y Formadas), que consisten en el uso simultáneo de calor instantáneo y fuerza centrífuga, usando equipo de diseño patentado, para convertir sistemas de polvo seco en micropartículas de tamaño y forma uniformes. La producción de micropartículas que contienen un fármaco activo usando esta tecnología CEFORM™ se describe en la patente de los Estados Unidos N° 5,683,720. Esta patente trata el uso del proceso LIQUIFLASH® para esferonizar composiciones que contienen uno o más fármacos activos para formar micropartículas LIQUIFLASH®.

Con la tecnología CEFORM™, el procesamiento de las micropartículas que contienen fármaco de la presente invención se lleva a cabo de manera continua, para lo cual una premezcla del fármaco y los excipientes se introduce en un "cabezal de microsfera" rotatorio, también denominada "cabezal de esferonización". El cabezal de microsfera, que es una unidad de producción multiabertura, gira sobre sus ejes y se calienta mediante energía eléctrica. La premezcla de fármaco y excipiente(s) se introduce en el centro del cabezal con un alimentador automatizado. El material se mueve, mediante fuerza centrífuga, al borde exterior donde los

calentadores, ubicados en el borde del cabezal, calientan el material. Las micropartículas se forman cuando el material fundido sale del cabezal, y luego son enfriadas por convección a medida que caen al fondo de la Cámara de Micropartículas. Después el producto se recoge y se almacena en los envases del producto adecuados. La selección cuidadosa de los tipos y los niveles del o de los excipientes controla las propiedades de las micropartículas como esfericidad, morfología superficial y velocidad de disolución. Una ventaja de dicho proceso es que las micropartículas se producen y se recogen de una carga de alimentación seca sin usar ningún disolvente.

Hay al menos dos métodos que se pueden usar para producir micropartículas que contienen fármaco usando el proceso de CEFORM: (i) el método de encapsulación y (ii) el método de co-fusión. En el método de encapsulación, el proceso se lleva a cabo por debajo del punto de fusión del fármaco. Por consiguiente, los excipientes se diseñan para fundir y arrastrar las partículas de fármaco al pasar a través de las aberturas para formar micropartículas. Las micropartículas resultantes contienen el fármaco, en su estado natural, esencialmente envuelto por o como una matriz íntima con los excipientes resolidificados. En el método de co-fusión, el proceso se lleva a cabo por encima del punto de fusión del fármaco. En este caso, el fármaco y los excipientes se funden o se convierten en líquido simultáneamente al exponerse al calor. La mezcla fundida sale del cabezal y forma micropartículas, que se enfrían a medida que caen al fondo de la cuba de depósito donde se recogen.

En al menos una realización las micropartículas se preparan usando el método de encapsulación. En el método de encapsulación el o los excipientes que se eligen tienen un punto de fusión inferior al del fármaco con el que se combinarán. Por consiguiente el proceso de esferonización se puede realizar a temperaturas inferiores, que el punto de fusión del fármaco. Como resultado, esto puede reducir el riesgo de interconversión polimérica, que puede ocurrir cuando se usan temperaturas de procesamiento próximas al punto de fusión.

En un ejemplo profético de ciertas realizaciones de la presente invención, el proceso de fabricación de las micropartículas puede ser hipotéticamente el siguiente: Se tamiza el auxiliar de esferonización a través de un tamiz de 425 micras (μm). En al menos una realización, el auxiliar de esferonización es monoestearato de glicerilo destilado (es decir DMG-03VF). Se agrega 50 % del auxiliar de esferonización a un bol de un mezclador de alto cizallamiento. En al menos una realización, el bol es un bol de 6 litros y el mezclador de alto cizallamiento es un granulador mezclador de alta velocidad Diosna P1-6. Después se agrega el fármaco activo al bol del mezclador, y después se agrega el resto del auxiliar de esferonización. Después se mezcla el material en el mezclador durante un tiempo entre 1 minuto y 30 minutos; preferentemente entre 3 minutos y 10 minutos; y más preferentemente durante 6 minutos. La velocidad del motor del mezclador es de 50 rpm a 2.000 rpm; preferentemente de 200 rpm a 500 rpm; y más preferentemente de 300 rpm. La velocidad del motor de la cortadora es de 50 rpm a 2.000 rpm; preferentemente de 200 rpm a 500 rpm; y más preferentemente de 400 rpm. El material mezclado se esferoniza a continuación en un cabezal de esferonización CEFORM™. La velocidad del cabezal de esferonización es de 5 Hz a 60 Hz; preferentemente de 10 Hz a 30 Hz; y más preferentemente de 15 Hz. En al menos una realización el cabezal de esferonización CEFORM™ es un cabezal de 5 pulgadas. La temperatura del cabezal de esferonización se mantiene de 70°C a 130°C; preferentemente de 90°C a 110°C; y más preferentemente a 100°C. Las micropartículas obtenidas a partir del proceso rotatorio se tamizan después a través de un tamiz que es de 150 μm a 800 μm.

Las micropartículas elaboradas usando un proceso de esferonización como el proceso CEFORM™, incluyen, además de la sal de bupropion, al menos un auxiliar de esferonización. Los auxiliares de esferonización pueden ayudar a la mezcla que contiene fármaco a formar partículas esféricas resistentes, duraderas. Algunos ejemplos de los materiales útiles como auxiliares de esferonización incluyen, pero no exclusivamente, monoestearato de glicerilo, behenato de glicerilo,

dibehenato de glicerilo, palmitoestearato de glicerilo, aceites hidrogenados como el aceite de ricino hidrogenado comercializado con el nombre Cutina™ HR, sales de ácidos grasos como estearato de magnesio o estearato de calcio, polioles como manitol, sorbitol, xilitol, ácido esteárico, ácido palmítico, lauril sulfato de sodio, éteres polioxietilénicos, polioxietilenos esterificados como distearato de PEG-32, distearato de PEG-150, alcohol cetoestearílico, ceras (por ejemplo, cera carnauba, cera blanca, cera de parafina) y materiales semejantes a cera. Ciertos polímeros termoplásticos o ablandados por calor también pueden actuar como auxiliares de esferonización. Algunos ejemplos no limitantes de dichos polímeros termoplásticos o ablandados por el calor incluyen povidona, éteres de celulosa y alcoholes polivinílicos. Se pueden usar combinaciones de auxiliares de esferonización. En al menos una realización, el auxiliar de esferonización es monoestearato de glicerilo (es decir DMG-03VF). El auxiliar de esferonización puede estar presente en una cantidad entre 0,1 % y 99 % en peso de la micropartícula. Por ejemplo, en ciertas realizaciones el auxiliar de esferonización está presente en una cantidad de 5 % a 90 %; en otras realizaciones de 10 % a 80 %; aún en otras realizaciones de 20 % a 70 %; y todavía en otras realizaciones de 30 % a 60 % en peso de la micropartícula. En al menos una realización el auxiliar de esferonización está presente en una cantidad de 50 % en peso de la micropartícula. En al menos otra realización, las micropartículas incluyen 50 % (p/p) de bromhidrato de bupropion y 50 % (p/p) del auxiliar de esferonización.

En ciertas realizaciones, cada micropartícula también puede incluir al menos un 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 hidrófilos se pueden usar para proporcionar a las composiciones cualquiera de varias características ventajosas, incluidas: mayor solubilidad de la sal de buproprion en la micropartícula; mejor disolución de la sal de buproprion; mejor solubilización de la sal de buproprion al disolverse; mejor absorción y/o biodisponibilidad de

la sal de buproprion. El tensioactivo hidrófilo puede ser un único tensioactivo hidrófilo o una mezcla de tensioactivos hidrófilos y puede ser iónico o no iónico.

Asimismo, otras varias realizaciones de la invención incluyen un componente lipófilo, que puede ser un tensioactivo lipófilo, incluida una mezcla de tensioactivos lipófilos, un triglicérido o una mezcla de éstos. El tensioactivo lipófilo puede proporcionar cualquiera de las características ventajosas mencionadas antes para los tensioactivo hidrófilos, así como mejorar aún más la función de los tensioactivos. Estas diversas realizaciones se describen en más detalle a continuación.

Como es bien conocido en el área, los términos "hidrófilos" y "lipófilos" son términos relativos. Para actuar como un tensioactivo, un compuesto incluye porciones polares o hidrófilas cargadas así como porciones apolares hidrófobas (lipófilas); es decir, un compuesto tensioactivo es anfifílico. Un parámetro empírico comúnmente utilizado para caracterizar la hidrofilicidad y lipofilicidad relativas de los compuestos anfifílicos no iónicos es el equilibrio hidrofílico-lipofílico (el valor "EHL"). Los tensioactivos con valores de EHL bajos son más lipófilos y tienen mayor solubilidad en los aceites, mientras que los tensioactivos con valores de EHL mayores son más hidrófilos y tienen mayor solubilidad en las soluciones acuosas.

Usando los valores de EHL como una guía aproximada, se puede considerar que los tensioactivos hidrófilos son en general los compuestos que tienen un valor de EHL superior a 10, así como los compuestos aniónicos, catiónicos o zwiteriónicos para los cuales no es aplicable la escala de EHL. De la misma manera, los tensioactivos lipófilos pueden ser los compuestos que tienen un valor de EHL menor de 10.

Se debe apreciar que el valor de EHL de un tensioactivo es sólo una guía aproximada que se usa generalmente para permitir la formulación de emulsiones industriales, farmacéuticas y cosméticas. Para muchos tensioactivos importantes, incluidos varios tensioactivos

polietoxilados, se ha informado que los valores de EHL pueden diferir hasta en 8 unidades de EHL, dependiendo del método empírico elegido para determinar el valor de EHL (Schott, J. Pharm. Sciences, 79(1), 87-88 (1990)). Asimismo, para ciertos copolímeros en bloque que contienen óxido de polipropileno (poloxámeros, que se comercializan como tensioactivos PLURONIC®, BASF Corp.), los valores de EHL pueden no reflejar con exactitud la naturaleza físicoquímica verdadera de los compuestos. Finalmente, los productos tensioactivos comerciales generalmente no son compuestos puros, sino que a menudo son mezclas complejas de compuestos y el valor de EHL informado para un compuesto en particular puede ser más exactamente característico del producto comercial del cual el compuesto es un componente principal. Diferentes productos comerciales que tienen el mismo componente tensioactivo principal pueden, y generalmente es así, tener diferentes valores de EHL. Además, se espera una cierta cantidad de variabilidad de lote-a-lote incluso para un único producto tensioactivo comercial. Teniendo estas dificultades inherentes en mente y usando los valores de EHL como una guía, un técnico con experiencia puede identificar fácilmente los tensioactivos que tienen la hidrofilicidad o lipofilicidad adecuadas para usar en la presente invención, según se describe aquí.

Los potenciadores de la solubilidad pueden ser cualquier tensioactivo adecuado para usar en las composiciones farmacéuticas. Los tensioactivos adecuados pueden ser aniónicos, catiónicos, zwiteriónicos o no iónicos. Dichos tensioactivos se pueden agrupar en las siguientes clases químicas generales detalladas en las tablas 81-98. Los valores de EHL de las tablas 81-98 que están más adelante representan en general el valor de EHL informado por el fabricante del producto comercial correspondiente. En los casos en que se indica más de un producto comercial, el valor de EHL de las tablas es el valor informado para uno de los productos comerciales, un promedio aproximado de los valores informados, o un valor que, a juicio de los presentes inventores, es más confiable.

Debe recalcarse que la invención no está limitada a los tensioactivos de las tablas 81-98, que muestran listas representativas, pero no exclusivas, de los tensioactivos

disponibles. Además, los tensioactivos refinados, destilados o fraccionados, sus fracciones purificadas o reesterificadas, están también dentro del alcance de la invención, aunque no se los indique específicamente en las tablas.

Aunque el polietilenglicol (PEG) en sí no funciona como un tensioactivo, hay diversos ésteres de ácidos grasos con PEG que tienen propiedades tensioactivas útiles. En la tabla 81 se muestran ejemplos de tensioactivos monoéster de ácidos grasos polietoxilados comercialmente disponibles.

Los diésteres de ácidos grasos de polietilenglicol (PEG) también son adecuados para usar como tensioactivos en las composiciones de la presente invención. En la tabla 82 se muestran diésteres de ácidos grasos de PEG representativos.

En general, las mezclas de tensioactivos también son útiles para la presente invención, incluidas mezclas de dos o más productos tensioactivos comerciales. Varios ésteres de ácidos grasos de PEG se comercializan como mezclas de mono y di ésteres. En la tabla 83 se muestran mezclas tensioactivas representativas.

En la tabla 84 se muestran ésteres de ácidos grasos de PEG glicerol adecuados.

Se puede prepar un gran número de tensioactivos de diferentes grados de lipofilicidad o hidrofilicidad mediante la reacción de alcoholes o polioles con una diversidad de aceites naturales y/o hidrogenados. En ciertas realizaciones, los aceites usados son aceite de ricino o aceite de ricino hidrogenado o un aceite vegetal comestible como aceite de maíz, aceite de oliva, aceite de maní, aceite de almendra de palma, el aceite de grano de albaricoque o aceite de almendra. Los ejemplos de alcoholes incluyen glicerol, propilenglicol, etilenglicol, polietilenglicol, sorbitol y pentaeritritol. En la tabla 85 se muestran tensioactivos representativos de esta clase adecuados para usar en la presente invención.

Los ésteres de ácidos grasos de poliglicerol también son tensioactivos adecuados para la presente invención. En la tabla 86 se muestran ejemplos de ésteres de poliglicerilo adecuados.

Los ésteres de ácidos grasos de propilenglicol son tensioactivos adecuados para usar en la presente invención. En la tabla 87 se dan ejemplos de tensioactivos de esta clase.

En general, las mezclas de tensioactivos también son adecuadas para usar en la presente invención. En particular, las mezclas de ésteres de ácidos grasos de propilenglicol y ésteres de ácidos grasos de glicerol son adecuadas y están disponibles comercialmente. En la tabla 88 se muestran ejemplos de estos tensioactivos.

Otra clase de tensioactivos es la clase de los mono y diglicéridos. Estos tensioactivos generalmente son lipófilos. En la Tabla 89 se dan ejemplos de estos tensioactivos.

Los esteroles y los derivados de los esteroles son tensioactivos adecuados para usar en la presente invención. Estos tensioactivos pueden ser hidrófilos o lipófilos. En la tabla 90 se muestran ejemplos de tensioactivos de esta clase.

Se dispone de una diversidad de ésteres de ácidos grasos de PEG-sorbitán que son adecuados para usar como tensioactivos en la presente invención. En general, estos tensioactivos son hidrófilos, aunque se pueden usar varios tensioactivos lipófilos de esta clase. En la tabla 91 se muestran ejemplos de estos tensioactivos.

Los éteres de polietilenglicol y alquilalcoholes son tensioactivos adecuados para usar en la presente invención. En la tabla 92 se muestran ejemplos de estos tensioactivos.

Los ésteres de azúcares son tensioactivos adecuados para usar en la presente invención. En la tabla 93 se muestran ejemplos de dichos tensioactivos.

Se dispone de varios tensioactivos hidrófilos PEG-alquilfenol que son adecuados para usar en la presente invención. En la tabla 94 se muestran ejemplos de estos tensioactivos.

Los copolímeros en bloque de OPE-OPP son una clase única de tensioactivos poliméricos. La estructura única 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 comercializan con diversos nombres comerciales, incluidos la serie Synperonic™ PE (ICI); la serie Pluronic® (BASF), Emkalyx™, Lutrol™ (BASF), Supronic™, Monolan™, Pluracare™ y Plurodac™. El término genérico para estos polímeros es "poloxámero" (CAS 9003-11-6). Estos polímeros tienen la fórmula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

donde "a" y "b" indican el número de unidades de polioxietileno y de polioxipropileno, respectivamente. En la tabla 95 se muestran ejemplos de tensioactivos adecuados de esta clase.

Los ésteres de ácidos grasos de sorbitán son tensioactivos adecuados para usar en la presente invención. En la tabla 96 se muestran ejemplos de estos tensioactivos.

Los ésteres de alcoholes inferiores (C_2 a C_4) y ácidos grasos (C_8 a C_{18}) son tensioactivo adecuados para usar en la presente invención. En la tabla 97 se muestran ejemplos de estos tensioactivos.

Los tensioactivos iónicos, incluidos los tensioactivos catiónicos, aniónicos y zwiteriónicos, son tensioactivos hidrófilos adecuados para usar en la presente invención. En ciertas realizaciones, el tensioactivo es un tensioactivo aniónico como una sal de un ácido graso, una sal biliar o una combinación de éstas. En otras realizaciones el tensioactivo es un tensioactivo catiónico como una carnitina. Los ejemplos de tensioactivos iónicos 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 carnitina; y miristoil carnitina. En la tabla 98 se muestran ejemplos de dichos tensioactivos.

Los tensioactivos ionizables, cuando están presentes en su forma no ionizada (neutra, no salina), son tensioactivos lipófilos adecuados para usar en las composiciones de la presente invención. Ejemplos particulares de dichos tensioactivos incluyen ácidos grasos libres, en particular ácidos grasos C_6-C_{22}, y ácidos biliares. Más específicamente, los tensioactivos ionizables sin ionizar adecuados incluyen las formas ácido graso libre y ácido biliar de cualquiera de las sales del ácido graso y las sales biliares que se muestran en la tabla 98.

Los derivados de las vitaminas liposolubles, como las vitaminas A, D, E, K, etc., también son tensioactivos útiles para las composiciones de la presente invención. Un ejemplo de dichos derivados es tocoferil PEG-1.000 succinato (TPGS, comercializado por Eastman).

En ciertas realizaciones, se usan tensioactivos o mezclas de tensioactivos que solidifican a temperatura ambiente. En otras realizaciones, se usan tensioactivos o mezclas de tensioactivos que solidifican a temperatura ambiente en combinación con componentes lipófilos particulares, como triglicéridos, o con adición de aditivos apropiados, como modificadores de la viscosidad, aglutinantes, espesantes y similares.

Los ejemplos de tensioactivos hidrófilos no iónicos incluyen alquilglucósidos; alquilmaltósidos; alquiltioglucósidos; lauril macrogolglicéridos; éteres polioxietilen alquílicos; polioxietilen alquilfenoles; ésteres de ácidos grasos de polietilenglicol; ésteres de ácidos grasos de polietilenglicol glicerol; ésteres de ácidos grasos de polioxietilen sorbitán; copolímeros en bloque de polioxietileno-polioxipropileno; ésteres de ácidos grasos de poliglicerol; polioxietilen glicéridos; polioxietilen esteroles, sus derivados y sus análogos; aceites vegetales polioxietilenados; aceites vegetales hidrogenados polioxietilenados; mezclas de reacción de polioles con ácidos grasos, glicéridos, aceites

vegetales, aceites vegetales hidrogenados y esteroles; ésteres de azúcares, éteres de azúcares; sucroglicéridos; vitaminas solubles en grasas polietoxiladas o sus derivados; y sus mezclas.

En ciertas realizaciones, el tensioactivo hidrófilo no iónico se selecciona del grupo que consiste en éteres polioxietilen alquílicos; ésteres de ácidos grasos de polietilenglicol; ésteres de ácidos grasos de polietilenglicol y glicerol; ésteres de ácidos grasos de polioxietilen sorbitán; copolímeros en bloque de polioxietileno-polioxipropileno; ésteres de ácidos grasos de poliglicerilo; polioxietilen glicéridos; aceites vegetales polioxietilenados; y aceites vegetales hidrogenados polioxietilenados. El glicérido puede ser un monoglicérido, diglicérido, triglicérido o una mezcla de estos.

En ciertas otras realizaciones, los tensioactivos usados son tensioactivos hidrófilos no iónicos que son mezclas de reacción de polioles y ácidos grasos, glicéridos, aceites vegetales, aceites vegetales hidrogenados o esteroles. Estas mezclas de reacción están compuestas en gran parte de los productos de transesterificación de la reacción, junto con mezclas a menudo complejas de otros productos de reacción. El poliol puede ser glicerol, etilenglicol, polietilenglicol, sorbitol, propilenglicol, pentaeritritol, un sacárido o una mezcla de éstos.

El tensioactivo hidrófilo también puede ser, o incluir como un componente, un tensioactivo iónico. Los ejemplos de tensioactivos iónicos incluyen sales de alquilamonio; sales y ácidos biliares, sus análogos y sus derivados; ácido fusídico y sus derivados; derivados ácidos grasos de aminoácidos, oligopéptidos y polipéptidos; derivados glicéridos de aminoácidos, oligopétidos y polipéptidos; lactilatos de acilo; ésteres de ácido tartárico mono y diacetilados de mono y diglicéridos; monoglicéridos succinilados; ésteres de ácido cítrico de mono y diglicéridos; sales de alginato; alginato de propilenglicol; lecitinas y lecitinas hidrogenadas; lisolecitina y lisolecitinas hidrogenadas; lisofosfolípidos y sus derivados; fosfolípidos y sus derivados; sales de alquilsulfatos; sales de ácidos

grasos; docusato de sodio; carnitinas; y mezclas de éstos.

En ciertas realizaciones los tensioactivos iónicos incluyen sales y ácidos biliares, sus análogos y sus derivados; lecitinas, lisolecitinas, fosfolípidos, lisofosfolípidos y sus derivados; sales de alquilsulfatos; sales de ácidos grasos; docusato de sodio; lactilatos de acilo; ésteres de ácido tartárico mono y diacetilados de mono y diglicéridos; monoglicéridos succinilados; ésteres de ácido cítrico de mono, diglicéridos; carnitinas; y sus mezclas.

Los ejemplos de tensioactivos iónicos incluyen lecitina, lisolecitina, fosfatidilcolina, fosfatidiletanolamina, fosfatidilglicerol, ácido fosfatídico, fosfatidilserina, lisofosfatidilcolina, lisofosfatidiletanolamina, lisofosfatidilglicerol, ácido lisofosfatídico, lisofosfatidilserina, PEG-fosfatidiletanolamina, PVP-fosfatidiletanolamina, ésteres lactílicos de ácidos grasos, estearoil-2-lactilato, estearoil lactilato, monoglicéridos succinilados, ésteres de ácido tartárico mono/diacetilados de mono/diglicéridos, ésteres de ácido cítrico de mono/diglicéridos, colato, taurocolato, glicocolato, desoxicolato, taurodesoxicolato, quenodesoxicolato, glicodesoxicolato, glicoquenodesoxicolato, 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.

En ciertas realizaciones, los tensioactivos iónicos usados incluyen lecitina, lisolecitina, fosfatidilcolina, fosfatidiletanolamina, fosfatidilglicerol, lisofosfatidilcolina, PEG-fosfatidiletanolamina, ésteres lactílicos de ácidos grasos, estearoil-2-lactilato, estearoil lactilato, monoglicéridos succinilados, ésteres de ácido tartárico mono/diacetilados de mono/diglicéridos, ésteres de ácido cítrico de mono/diglicéridos, colato, taurocolato, glicocolato,

desoxicolato, taurodesoxicolato, glicodesoxicolato, colilsarcosina, caproato, caprilato, caprato, laurato, oleato, lauril sulfato, docusato y sus sales y mezclas. En al menos una realización, el tensioactivo iónico se selecciona entre lecitina, ésteres lactílicos de ácidos grasos, estearoil-2-lactilato, estearoil lactilato, monoglicéridos succinilados, ésteres del ácido tartárico mono/diacetilados de mono/diglicéridos, ésteres de ácido cítrico de mono/diglicéridos, taurocolato, caprilato, caprato, oleato, lauril sulfato, docusato y sus sales y mezclas.

Los ejemplos de tensioactivos lipófilos incluyen alcoholes; éteres polioxietilen alquílicos; ácidos grasos; ésteres de ácidos grasos de glicerol; ésteres de ácidos grasos de glicerol acetilados; ésteres de ácidos grasos de alcoholes inferiores; ésteres de ácidos grasos de polietilenglicol; ésteres de ácidos grasos de polietilenglicol glicerol; ésteres de ácidos grasos de polipropilenglicol; polioxietilen glicéridos; derivados de ácido láctico de mono/diglicéridos; propilenglicol diglicéridos; ésteres de ácidos grasos de sorbitán; ésteres de ácidos grasos de polioxietilen sorbitán; copolímeros en bloque de polioxietileno-polioxipropileno; aceites vegetales transesterificados; esteroles; derivados de esteroles; ésteres de azúcares; éteres de azúcares; sucroglicéridos; aceites vegetales polioxietilenados; aceites vegetales hidrogenados polioxietilenados; y sus mezclas.

Al igual que los tensioactivo hidrófilos, los tensioactivos lipófilos pueden ser mezclas de reacción de polioles y ácidos grasos, glicéridos, aceites vegetales, aceites vegetales hidrogenados y esteroles.

En ciertas realizaciones, los tensioactivos lipófilos incluyen uno o más seleccionados del grupo que consiste en ácidos grasos; ésteres de ácidos grasos de alcoholes inferiores; ésteres de ácidos grasos de polietilenglicol glicerol; ésteres de ácidos grasos de polipropilenglicol; polioxietilen glicéridos; ésteres de ácidos grasos de glicerol; ésteres de ácidos grasos de glicerol acetilados; derivados de ácido láctico de mono/diglicéridos; ésteres de ácidos grasos de sorbitán;

ésteres de ácidos grasos de polioxietilen sorbitán; copolímeros en bloque de polioxietileno-polioxipropileno; aceites vegetales polioxietilenados; aceites vegetales hidrogenados polioxietilenados; y mezclas de reacción de polioles y ácidos grasos, glicéridos, aceites vegetales, aceites vegetales hidrogenados, esteroles y sus mezclas.

En ciertas otras realizaciones, los tensioactivos lipófilos incluyen uno o más seleccionados del grupo que consiste en ésteres de ácidos grasos de alcoholes inferiores; ésteres de ácidos grasos de polipropilenglicol; ésteres de ácidos grasos de prolilenglicol: ésteres de ácidos grasos de glicerol; ésteres de ácidos grasos de glicerol acetilados; derivados de ácido láctico de mono/diglicéridos; ésteres de ácidos grasos de sorbitán; aceites vegetales polioxietilenados; y sus mezclas. Entre los ésteres de ácidos grasos de glicerol, los ésteres pueden ser mono o diglicéridos, o mezclas de mono y diglicéridos, donde la porción ácido graso es un ácido graso C_6 a C_{22}.

Otras realizaciones incluyen tensioactivos lipófilos que son la mezcla de reacciones de polioles y ácidos grasos, glicéridos, aceites vegetales, aceites vegetales hidrogenados y esteroles. Los ejemplos de los polioles son polietilenglicol, sorbitol, propilenglicol, pentaeritritol y sus mezclas.

Se pueden usar combinaciones de los potenciadores de la solubilidad (es decir tensioactivos). Los ejemplos de ésteres de ácidos grasos de macrogol útiles como potenciadores de la solubilidad incluyen Gelucire 50/13® y Gelucire 44/14®. En al menos una realización el potenciador de la solubilidad es Gelucire 50/13®. El potenciador de la solubilidad puede estar presente en una cantidad entre 0,1 % y 70 % en peso de la micropartícula. Por ejemplo, en ciertas realizaciones, el potenciador de la solubilidad está presente en una cantidad entre 1 % y 50 %; en otras realizaciones entre 10 % y 30 %; en aún otras realizaciones entre 15 % y 25 % en peso de la micropartícula. En al menos una realización el potenciador de la solubilidad está presente en una cantidad de 20 % en peso de la micropartícula.

Se contempla que en algunas realizaciones se pueden usar en las micropartículas, uno o más de otros excipientes farmacéuticamente aceptables compatibles con los objetivos de la presente invención, como un lubricante, un aglutinante, un modificador del pH, un relleno y/o un deslizante.

Los procesos para elaborar las micropartículas que contienen fármaco de la presente invención por esferonización no están restringidos a la tecnología CEFORM™ y también se puede usar cualquier otra tecnología que dé como resultado la formación de las micropartículas compatibles con los objetivos de la presente invención. Por ejemplo, las micropartículas de la invención también se pueden elaborar por extrusión/esferonización, granulación o peletización.

Extrusión/esferonización es un proceso multipasos usado para hacer partículas esféricas de tamaño uniforme. La técnica ofrece la capacidad de incorporar niveles altos de ingredientes activos sin producir partículas excesivamente grandes. Los pasos principales del proceso son:

(i) Mezcla en seco de los ingredientes para lograr una dispersión de polvos homogénea;
(ii) Amasado en húmedo usando por ejemplo un granulador de alto cizallamiento en húmedo para formar partículas en forma de varilla de diámetro uniforme;
(iii) Extrusión para formar partículas en forma de varilla de diámetro uniforme;
(iv) Esferonización para redondear las varillas en partículas esféricas;
(v) Tamización para lograr la distribución estrecha de tamaños de la partícula deseada.

El recipiente de mezcla usado para la mezcla en seco puede ser de cualquier tamaño y forma compatible con el tamaño de la formulación que se va a producir. Por ejemplo, se pueden usar dispositivos de mezcla comercialmente disponibles como los mezcladores planetarios, los mezcladores de alto cizallamiento o los mezcladores de dos conos. Si se van a preparar cantidades relativamente pequeñas de formulación, un simple mortero

con su mano pueden ser suficientes para mezclar los ingredientes. El tipo de recipiente de mezcla será evidente para un técnico con experiencia en el área farmacéutica. La masa humedecida formada por amasado en húmedo en un equipo de granulación convencional se extruye a través de una malla perforada para producir filamentos cilíndricos. El orificio de las mallas puede determinar el diámetro de los filamentos. Se puede usar un orificio que varíe de 0,2 mm a 3 mm en este proceso. En al menos una realización que utiliza este proceso, el orificio varía de 0,4 mm a 2 mm. La extrusión se puede llevar a cabo usando extrusoras de tornillo, de doble tornillo, del tipo "cedazo y cesta", "extrusora de rodillo", "extrusora de pisones" o cualquier otro medio farmacéuticamente aceptable para producir filamentos cilíndricos. En ciertas realizaciones que utilizan este proceso de extrusión/esferonización, se usa una extrusora coaxial de tornillo doble. El dispositivo de esferonización comprende un cilindro hueco con una placa rotatoria horizontal. Los filamentos se rompen en segmentos cortos que se transforman en partículas esféricas o cuasiesféricas en la superficie superior de la placa rotatoria a una velocidad que varía de 200 rpm a 2.000 rpm. Las partículas se pueden secar de cualquier manera farmacéuticamente aceptable, como por ejemplo por secado en aire en una condición estática. Las partículas se usan como están o se recubren para obtener gránulos para usar en los comprimidos, las cápsulas, bolsitas u otras formulaciones farmacéuticas.

Un ejemplo profético de una formulación 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 1 % y 80 % p/p. En ciertas realizaciones dentro de este ejemplo, el bromhidrato de bupropion está presente en una cantidad entre 1 % y 50 % p/p; en otras realizaciones entre 10 % y 30 %; y aún en otras realizaciones en 10 % p/p. En este ejemplo, el relleno puede estar presente en una cantidad entre 0 % y 80 % p/p. En ciertas realizaciones de este ejemplo, el relleno está presente en una cantidad entre 10 % y 60 %; y en otras realizaciones en 40 % p/p. En este ejemplo, la celulosa microcristalina puede estar presente en una

cantidad entre 10 % y 90 % p/p. En ciertas realizaciones de este ejemplo, la celulosa microcristalina está presente en una cantidad entre 10 % y 70 %; y en otras realizaciones entre 20 % y 50 % p/p. En este ejemplo, el aglutinante puede estar presente en una cantidad entre 0 % y 10 % p/p. En ciertas realizaciones de este ejemplo, el aglutinante está presente en una cantidad entre 1 % y 8 %; y en otras realizaciones entre 2 % y 4 % p/p. En este ejemplo, el agua puede estar presente en una cantidad entre 10 % y 80 % p/p. En ciertas realizaciones de este ejemplo, el agua está presente en una cantidad entre 15 % y 70 %; y en otras realizaciones entre 20 % y 50 % p/p. Los rellenos adecuados en este ejemplo incluyen, pero no exclusivamente, fosfato dibásico de calcio, fosfato tricálcico, carbonato de calcio, almidón (como almidones de maíz, papa y arroz), almidones modificados (como carboximetilalmidón, etc.), celulosa microcristalina, sacarosa, dextrosa, maltodextrinas, lactosa y fructosa. Los lubricantes adecuados en este ejemplo incluyen, pero no exclusivamente, estearatos metálicos (como estearatos de calcio, magnesio o cinc), ácido esteárico, aceites vegetales hidrogenados, talco, almidón, aceite mineral ligero, benzoato de sodio, cloruro de sodio, lauril sulfato de sodio, lauril sulfato de magnesio, estearil fumarato de sodio, behenato de glicerilo y polietilenglicol (como Carbowax™ 4000 y 6000). Los antiantiadherentes adecuados en este ejemplo incluyen, pero no exclusivamente, al dióxido de silicio coloidal. Los aglutinantes adecuados en este ejemplo incluyen, pero no exclusivamente, etilcelulosa, un polímero de polimetacrilato, alcohol polivinílico, polivinilpirrolidona, copolímero de polivinilpirrolidona-acetato de vinilo (por ejemplo, Kollidon VA64) hidroxietilcelulosa, hidroxipropilmetilcelulosa de bajo peso molecular (por ejemplo, viscosidad de 1-50 cp a 20 °C; 2-12 cp a 20 °C; o 4-6 cp a 20 °C), polimetacrilatos de hidroxipropilcelulosa y sus mezclas.

Las micropartículas que contienen fármaco formadas por extrusión/esferonización en este ejemplo profético se pueden producir usando polímeros anfifílicos reticulados mediante los pasos siguientes: (a) mezcla de uno o más polímeros anfifílicos reticulados con bromhidrato de bupropion y opcionalmente otros excipientes farmacéuticos

para obtener una mezcla uniforme en forma de polvo seco al cual se agrega una cantidad adecuada de líquido para obtener una consistencia pastosa; (b) extrusión de la mezcla obtenida en el paso (a) a través de una malla perforada para obtener filamentos cilíndricos con la longitud y el diámetro deseados; (c) esferonización de los filamentos para obtener un producto en forma de multiparticulados esféricos; (d) secado del producto; y (e) colocación opcional de un fármaco sobre la superficie de las micropartículas. "Polímero anfifílico reticulado" hace referencia en este ejemplo a los polímeros que presentan características de hinchabilidad en todo el intervalo pH de las soluciones acuosas y también en disolventes o mezclas disolventes con características de polaridad diferentes. Los polímeros pueden ser reticulados ya sea físicamente a través de la interpenetración de las mallas macromoleculares, o químicamente, mostrando por lo tanto puntos de unión entre las cadenas macromoleculares. Los ejemplos no limitantes de dichos polímeros 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 distribución uniforme de cada componente. Un tiempo de mezcla razonable puede variar de 1 a 60 minutos 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 término "líquido" en este ejemplo significa cualquier sustancia líquida o mezcla (solución o emulsión) de líquidos de uso farmacéutico normal capaz de humedecer la mezcla de polvos, como por ejemplo agua, soluciones acuosas con diferente pH, disolventes orgánicos de uso farmacéutico normal (por ejemplo, alcoholes, disolventes clorados) y aceites. Entre los aceites y los tensioactivos que se pueden usar en este ejemplo están: los aceites naturales, ya sea saturados o insaturados (aceites de oliva, maní, soja, maíz, coco, palma, sésamo y similares); los mono, di y triglicéridos semisintéticos y sintéticos, que contienen ácidos grasos

saturados y/o insaturados y sus derivados polihidroxietilados (triglicéridos cáprico-caprílico [Mygliol™, Captex™, Labrafac™, Lipo], los triglicéridos polihidroxilados saturados o insaturados de diversas clases [Labrafil™, Labrafac™ Hydro, Gelucire™]); las ceras líquidas (miristato de isopropilo, caprinato de isopropilo, caprilato de isopropilo, laurato de isopropilo, palmitato de isopropilo, estearato de isopropilo); los ésteres de ácidos grasos (oleato de etilo, oleato de oleilo); los aceites de silicona; polietilenglicoles (PEG 200, PEG 400, PEG 600, PEG 1.000, y así sucesivamente); los glicéridos poliglicólicos (por ejemplo Labrasol™); los poliglicoles (propilenglicol, tetraglicol y etoxidiglicol (Transcutol™)), los ésteres de ácidos grasos de sorbitán (por ejemplo Span®, Arlacel®, Brij®), los ésteres de ácidos grasos de polioxietilensorbitán (por ejemplo Tween®, Capmul®, Liposorb®), los copolímeros de óxido de polipropileno-óxido de polietileno (Poloxamer), los ésteres del polietilenglicol (PEG)-glicerol (Labrasol®, Labrafil®), los ésteres de PEG y ácidos alifáticos o alcoholes de cadena larga (por ejemplo Cremophor®), los ésteres poliglicéridos (Plurol®), los ésteres sacáridos y de ácidos grasos (sucro-ésteres). Además, se pueden usar tensioactivos aniónicos (por ejemplo lauril sulfato de sodio, estearato de sodio, oleato de sodio) o tensioactivos catiónicos (por ejemplo tricetol), así como lecitinas, fosfolípidos y sus derivados semisintético o sintéticos. También el bromhidrato de bupropion y/o los excipientes se pueden disolver, dispersar y/o emulsionar en dichos líquidos.

En una realización particular formada por un proceso de extrusión/esferonización del ejemplo profético descrito anteriormente, el líquido humectante comprende un sistema aceite/tensioactivo en el que se disuelve o se dispersa el bromhidrato de bupropion opcionalmente emulsionado con una fase acuosa. La cantidad de líquido con respecto al sólido usada en la preparación de la mezcla puede variar de 1 % a 80 % en peso. Como un ejemplo profético de esta realización, una mezcla de bromhidrato de bupropion y Kollidon™ CL en una relación igual a 1/3 en peso se muele conjuntamente obteniéndose la mezcla en forma de polvo con 100 % de la granulometría inferior a 50 micras. La

mezcla se humedece usando agua desmineralizada que contiene Kollidon™ 25 (polivinilpirrolidona, BASF) en una solución al 3 % p/p. Se lleva a cabo la extrusión forzando la masa humedecida a través de una roscadora que tiene un diámetro de los orificios igual a 1 mm. Los parámetros operativos en este ejemplo profético pueden ser los siguientes: velocidad de flujo de polvo: 4,5 kg/h; velocidad de flujo del líquido: 4,1 kg/h; esfuerzo torsional: 27 %; temperatura de la cabeza: 46 °C; y la velocidad de rotación del tornillo: 140 rpm. Los filamentos de extrusión se procesan luego en un esferonizador ajustado a una velocidad igual a 1.000 rpm durante 2 minutos. Después las micropartículas obtenidas se secan en un lecho fluido durante 2 horas a una temperatura máxima igual a 59°C. Al final del secado el producto se descarga y se tamiza mecánicamente separando la fracción que varía de 0,7 mm a 1,2 mm.

Otro ejemplo profético de una realización de las micropartículas que contienen fármaco de la invención formadas por un proceso de extrusión/esferonización, usa una resina cargada, cuyos pasos pueden comprender: (a) agregar la resina cargada, el bromhidrato de bupropion y otros excipientes, a un recipiente de mezcla; (b) mezclar los ingredientes para obtener una mezcla uniforme; (c) agregar una solución de granulación o un líquido capaz de humedecer la mezcla seca. Se incluyen los líquidos que dan lugar a la conversión de la mezcla de polvos secos en una granulación húmeda que soporta la extrusión y esferonización posteriores (marumerización). Típicamente, se emplean agua o soluciones acuosas. Se pueden incluir alcoholes, típicamente etanol o isopropanol, con el agua de granulación para mejorar la maniobrabilidad de la granulación. En otra realización de esta invención, uno o más de los componentes de la formulación se disuelve primero en agua y esta solución se usa para producir la granulación húmeda. Un principio activo o un excipiente que está presente en una concentración muy baja se puede disolver o suspender inicialmente en el disolvente de granulación para asegurar la distribución más uniforme en toda la formulación; (d) granular la mezcla hasta que resulte una granulación uniforme; (e) extrudir la granulación húmeda a través de un tamiz para producir filamentos de granulación; (f) esferonizar los filamentos

de la granulación para producir multiparticulados esféricos; y (g) recoger y secar los multiparticulados esféricos. Por "resina cargada" se quiere dar a entender en este ejemplo un polímero con grupos funcionales ionizable que se torna útil en la realización de esta invención. Esto abarca ampliamente cualquier polímero que al ionizarse, es capaz de producir cadenas poliméricas catiónicas o aniónicas y que soporta esferonización. Típicamente de 10 % a 70 % en peso del multiparticulado esférico es resina cargada. Ejemplos no limitantes de estas resinas cargadas incluyen poliestiren sulfonato de sodio que se vende con el nombre comercial AMBERLITE IRP-69™ de Rohm y Haas, Co., Filadelfia, Pa.; la sal de cloruro de la resina colestiramina USP, que se vende como AMBERLITE IRP-276™ de Rohm y Haas, Co., Filadelfia, Pa.; la forma ácida de ácido metacrílico-divinil benceno, que se vende como AMBERLITE IRP-64™ by Rohm y Haas Co., Filadelfia, Pa.; carboxipolimetilenos que se venden con los nombres comerciales CARBOPOL™ 974P y CARBOPOL™ 934P de B.F. Goodrich, Inc., Brecksville, Ohio, y poliacrilato de sodio, que se vende con el nombre comercial AQUAKEEP™ J-550 de Seitetsu Kagaku, Japón. Para que la resina pueda mantener el grado de ionización deseado, se pueden incluir los agentes que producen un ambiente ácido o básico durante la granulación y la esferonización en la formulación. Entre los grupos de compuestos que pueden ejercer este efecto están los ácidos, las bases y las sales de ácidos y bases como ácido adípico, ácido cítrico, ácido fumárico, ácido tartárico, ácido succínico, carbonato de sodio, bicarbonato de sodio, citrato de sodio, acetato de sodio, fosfatos 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 el grado adecuado de hidratación de la resina cargada, el medicamento y los excipientes. Estos hidratantes incluyen azúcares como lactosa, sacarosa, manitol, sorbitol, pentaeritritol, glucosa y dextrosa. También se pueden usar polímeros como polietilenglicol así como tensioactivos y otras sales orgánicas e inorgánicas para modular la hidratación del polímero.

En otro ejemplo profético, se pueden obtener multiparticulados que contienen bromhidrato de bupropion del modo siguiente:

Componente	Porcentaje p/p
Bupropion HBr	8,7
Fosfato disódico	7,0
Fosfato monosódico	1,7
Dodecil sulfato de sodio	21,7
Cloruro de sodio	17,4
Povidona 29-32K	8,7
AMBERLITE IRP-69	34,8
Hidroxianisol butilado	0,0002

En este ejemplo profético, aproximadamente 5,75 kg de la formulación anterior se mezclan en un mezclador planetario durante 15 minutos. El hidroxianisol butilado se disuelve en 60 cc de etanol y se agrega agua para llevar la solución a un volumen final de 133 cc. Esta solución se agrega al mezclador planetario durante un período de dos (2) minutos. El mezclador se granula después con siete alícuotas de 250 cc de agua agregadas durante un período de quince minutos. La granulación así formada se extruye a través de un tamiz de 1,0 mm y las alícuotas se esferonizan por marumerización a aproximadamente 1.200 rpm durante aproximadamente 10 minutos cada una. Después los multiparticulados esféricos formados se secan a 50°C durante 24 horas.

Otra realización de esta invención implica la producción de micropartículas que contienen fármaco en forma de 'perlas'. Las perlas se pueden fabricar mezclando el bromhidrato de bupropion con uno o más excipientes farmacéuticos en forma fundida; la masa fundida se hace pasar a la fuerza a través de una boquilla sometida a una vibración; las perlas formadas se dejan caer en una torre a contracorriente a un gas; y las perlas sólidas se recogen en el fondo de la torre. En este ejemplo, la cantidad de bromhidrato de bupropion puede variar de 5 % a 95 % en peso; y en ciertas realizaciones de 40 % a 60 % en peso. Los aditivos que permiten inducir la cristalización del producto superenfriado en este ejemplo se pueden elegir entre los siguientes: alcoholes grasos como: alcohol cetílico, alcohol estearílico, ácidos grasos como: ácido esteárico, ácido palmítico, ésteres de glicerol como: palmitoestearato de glicerol, estearato de

glicerol que se comercializa bajo la marca Precirol™, behenato de glicerol que se comercializa bajo la marca Compritol™, aceites hidrogenados como: aceite de ricino hidrogenado que se comercializa bajo la marca Cutina™ HR, sales de ácidos grasos como: estearato de calcio o magnesio, polioles como: manitol, sorbitol, xilitol, ceras como: cera blanca, cera carnauba, cera de parafina, polioxitilenglicoles de alto peso molecular y polioxietilenos esterificados como: Diestearato de PEG-32 y diestearato de PEG-150. A estos aditivos de cristalización puede ser deseable en este ejemplo agregarles polímeros que son solubles o dispersable en la masa fundida y que proporcionan una disolución controlada y regulable de las perlas cuando se usan, cuyos ejemplos incluyen: derivados de celulosa (hidroxipropilcelulosa, hidroxipropilmetilcelulosa, hidroxietilcelulosa, etilcelulosa, carboximetilcelulosa), resinas acrílicas (comercializadas bajo la marca Eudragit®), acetatos polivinílicos (comercializados bajo la marca Rhodopas®), polialquileno (etileno, propileno), poliláctico, anhídrido maleico y resinas de silicona. Además, se pueden agregar aditivos inorgánicos para acelerar la solidificación de los principios activos, cuyos ejemplos incluyen: sílices, óxidos inorgánicos como óxido, de titanio o de hierro, fosfatos, carbonatos, arcillas y talco. Además, se puede agregar un agente de superficie para mejorar la dispersión de la sustancia activa en el aditivo de cristalización, cuyos ejemplos incluyen: ésteres de sorbitol, polisorbatos de polioxietileno que se comercializan bajo la marca Tween® y glicoles como glicerina o propilenglicol. El proceso para la preparación de las perlas comprende preparar una masa fundida del bromhidrato de bupropion con uno o más excipientes. Esta masa fundida se puede preparar fundiendo por separado diversos constituyentes y luego mezclándolos o fundiendo la mezcla de los constituyentes y agregando los posibles compuestos insolubles al final de la fusión para obtener una masa homogénea. El técnico con experiencia en el área 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 mezcla de los constituyentes, el diámetro de la boquilla, la hidrofilicidad del principio activo, la tensión superficial del principio activo, el

tamaño de partícula de los aditivos insolubles, la velocidad de flujo de la boquilla, la temperatura de la torre, su altura y, sobre todo, el tamaño deseado de las perlas, la proporción de bromhidrato de bupropion que se va a incluir y el tiempo de liberación del principio activo deseado.

Los procedimientos alternativos diferentes de la extrusión o la esferonización para preparar micropartículas que contienen droga pueden incluir granulación húmeda, granulación en disolvente y granulación por fusión. Todas estas técnicas implican la adición de un aglutinante inactivo para agregar las partículas más pequeñas en gránulos más grandes. Por ejemplo, la granulación húmeda y la granulación en disolvente implican la adición de un aglutinante líquido que agrege los materiales activos y los excipientes en gránulos. Después de la granulación, se puede eliminar el líquido mediante otro paso de secado. La granulación por fusión es similar a la granulación húmeda, pero usa un material sólido de bajo punto de fusión como aglutinante. El aglutinante sólido en la granulación por fusión se funde y actúa como un aglutinante líquido agregando de ese modo al principio activo y los excipientes en polvo en gránulos. De ese modo, el aglutinante se puede incorporar en los gránulos cuando los gránulos se enfrían.

Ciertas realizaciones de la presente invención incluyen micropartículas elaboradas por un proceso para producir gránulos por granulación en rotomelt que comprende la mezcla del bromhidrato de bupropion y de un material excipiente en polvo con un punto de fusión mayor que el bromhidrato de bupropion 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 rápidamente ubicado dentro de un recipiente vertical que tiene una superficie inferior; donde dicho disco que gira rápidamente está ubicado sobre la superficie inferior del recipiente vertical en el que dicho gas está a una temperatura suficiente para provocar la fusión al menos parcial del bromhidrato de bupropion haciendo de ese modo que dichos materiales en polvo se agreguen y formen

gránulos. Otras realizaciones de la presente invención incluyen micropartículas elaboradas mediante un proceso para producir gránulos por granulación en rotomelt que comprende mezclar el material aglutinante en polvo y el bromhidrato de bupropion, donde el bromhidrato de bupropion tiene un punto de fusión 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 rápidamente ubicado dentro de un recipiente vertical que tiene una superficie inferior; donde dicho disco que gira rápidamente está ubicado sobre la superficie inferior del recipiente vertical donde dicho gas está a una temperatura suficiente para provocar la fusión al menos parcial del material aglutinante haciendo de ese modo que dichos materiales en polvo se agreguen y formen gránulos.

En la granulación en rotomelt, uno de los polvos de alimentación debe tener un punto de fusión inferior que el otro polvo para servir como aglutinante. Los polvos de alimentación se introducen en un recipiente vertical con un disco horizontal que gira ubicado en el fondo del recipiente. El polvo se mantiene en estado fluidizado mediante al menos una corriente de aire filtrado que se hace circular desde el fondo del recipiente vertical a través de una o más entradas. Después se hace girar el disco horizontal giratorio mientras el aire provisto para fluidizar el polvo se mantiene a una temperatura suficiente para ablandar o fundir el polvo de menor punto de fusión. La temperatura a la cual se debe calentar el aglutinante para que se ablande se puede determinar empíricamente observando la formación de gránulos a diversas temperaturas para diversos aglutinantes. En la actualidad se cree que las temperaturas de 3°C a 5°C por debajo del punto de fusión o del intervalo de fusión proporcionan suficiente ablandamiento para dar lugar a la formación de gránulos. El polvo de menor punto de fusión actúa después como un aglutinante para promover la agregación de las partículas de polvo en gránulos. Los polvos adecuados para usar en la granulación con rotomelt tienen un tamaño de diámetro en el rango entre 5 micras y 150 micras; y en ciertas realizaciones tienen un tamaño de diámetro en el rango entre 35 micras y 80 micras. La

temperatura a la que se expondrán los componentes depende del aglutinante empleado para agregar los polvos. En general, el punto de fusión del aglutinante está por encima de 30°C; y en ciertas realizaciones está por debajo de 100°C.

Los polvos usados en estas micropartículas preparadas por granulación en rotomelt se pueden transformar en gránulos por al menos dos mecanismos de granulación alternativos. El primer mecanismo para la formación de gránulos utiliza un aglutinante particulado de mayor tamaño y un polvo particulado de menor tamaño. Después se eleva la temperatura durante la granulación en rotomelt sólo hasta el punto en el que la superficie externa de las partículas de aglutinante se vuelve pegajosa. A medida que el segundo material en polvo de un tamaño menor entra en contacto con la superficie pegajosa forma una microcapa sobre la superficie de la partícula de aglutinante. Este mecanismo de granulación da lugar a gránulos que tienen una distribución de tamaño similar a la de las partículas originales de aglutinante empleadas. Alternativamente, la granulación en rotomelt puede llevarse a cabo a una temperatura a la cual el aglutinante actúa como un cemento que forma puentes en los espacios entre las partículas sin fundir (esto se denomina aglomeración). Este mecanismo da lugar a la formación de gránulos donde los componentes se entremezclan. Para cada aglutinante usado el mecanismo se puede controlar principalmente mediante la temperatura a la cual se realiza la granulación en rotomelt. Los técnicos con experiencia en el área apreciarán que los gránulos formados se pueden observar por microscopia electrónica para determinar el tipo de proceso de granulación que ocurre. Si se desea un tipo particular de gránulo, se pueden variar las condiciones o los materiales de partida del proceso para producir los gránulos deseados.

En al menos una realización de la presente invención, el bromhidrato de bupropion se funde para actuar como un aglutinante en el proceso de granulación en rotomelt. Los ejemplos de excipientes adecuados incluyen los seleccionados entre los siguientes: rellenos, lubricantes, deslizantes y antiadherentes. Los rellenos

adecuados incluyen, pero no exclusivamente, fosfato dibásico de calcio, fosfato tricálcico, carbonato de calcio, almidón (como almidones de maíz, papa y arroz), almidones modificados (como carboximetilalmidón, etc.), celulosa microcristalina, sacarosa, dextrosa, maltodextrinas, lactosa y fructosa. La cantidad de aglutinante adicionada para agregar las partículas en gránulos puede variar entre 10 % p/p y 80 % p/p; y en ciertas realizaciones entre 30% p/p y 70% p/p de los materiales en polvo en la granulación en rotomelt. El porcentaje en peso restante para proporcionar un total de 100 % p/p puede ser uno o más principios activos farmacéuticos en polvo adecuados. Opcionalmente la granulación en rotomelt también puede contener de 0 % a 60 % p/p de uno o más excipientes en polvo donde el peso total de todos los materiales en polvo equivale a 100 % p/p. El aglutinante usado en estas realizaciones de la invención puede ser un polvo seco farmacéuticamente aceptable que tiene un tamaño de partícula que varía entre 5 µm y 150 µm; y en ciertas realizaciones entre 35 µm y 80 µm. Los aglutinantes adecuados para la granulación en rotomelt son aglutinantes de bajo punto de fusión, cuyos ejemplos incluyen: polietilenglicol 4000, polietilenglicol 6000, ácido esteárico y ceras de bajo punto de fusión. Las ceras adecuadas de bajo punto de fusión incluyen, pero no exclusivamente, monoestearato de glicerilo, sebo hidrogenado, alcohol miristílico, ácido mirístico, alcohol estearílico, monoglicéridos sustituidos, digliceridos sustituidos, triglicéridos sustituidos, cera blanca de abeja, cera carnauba, cera de ricino, cera de Japón, monoglicéridos acetilados y sus combinaciones. Los aglutinantes pueden tener un punto de fusión entre 30 °C y 100 °C; y en ciertas realizaciones entre 40 °C y 85 °C.

De acuerdo con un ejemplo profético de estas realizaciones preparadas mediante un proceso de granulación en rotomelt, se mezclan en seco 320 g de bromhidrato de bupropion y 80 g de PEG 8000 y se vierten en una cámara Glatt 1.1 ajustada como un granulador rotatorio con una placa longitudinal. La temperatura de entrada del aire se fija a 60°C y la cámara del producto se calienta aproximadamente a 50°C. La mezcla se fluidiza a aproximadamente 120 m^3/h y la placa friccional se fija a

900 rpm. La temperatura de la cámara del producto se eleva a 60°C y después se reduce gradualmente a 20°C durante un período de aproximadamente 20 minutos, durante el cual se logra la esferonización.

Otras realizaciones de la invención implican la formación de una micropartícula que tiene un núcleo que contiene bromhidrato de bupropion y un compuesto que es de sabor dulce y que tiene un calor de disolución negativo. Los ejemplos de los compuestos que se clasifican en esta categoría incluyen manitol y sorbitol. También pueden funcionar los azúcares o los edulcorantes artificiales a los cuales se les ha agregado, por ejemplo, mentol. También se pueden colocar un aglutinante y/o otro excipiente dentro del núcleo. La cantidad de edulcorante usada puede depender de varios factores incluidos el tamaño de las micropartículas resultantes, el tamaño o el volumen del comprimido resultante, la solidez del microparticulante de la micropartícula recubierta, la velocidad a la cual se desintegrará el comprimido en la boca, el grado de dulzura impartida por el edulcorante particular usado, en la micropartícula o en el comprimido, o ambos, y de la cantidad de fármaco usada y similares. Por ejemplo, las micropartículas particularmente resistentes pueden tener menor probabilidad de romperse durante la masticación y/o la compresión. Por consiguiente, se puede reducir la cantidad de material proporcionado para proteger 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 variará entre más de cero y 80 % del peso de las micropartículas resultantes. El edulcorante y el bromhidrato de bupropion se pueden combinar de cualquier manera conocida, como por ejemplo por granulación húmeda, granulación seca, aglomeración, o recubrimiento por pulverización. Por ejemplo, el edulcorante se puede usar como un adsorbente para el principio activo. Alternativamente, también se pueden mezclar juntas simplemente las partículas de cada uno. Asimismo, se pueden usar uno o más 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 10 % como una pasta acuosa); almidón pregelatinizado (por ejemplo, en una cantidad de 5 % a 10 % agregado seco al polvo); gelatina (por ejemplo, en una cantidad entre 2 % y 10 % como una solución acuosa, o 2 % en pasta de almidón); polivinilpirrolidona (por ejemplo, en una cantidad entre 2 % y 20 % en una solución acuosa o alcohólica); metilcelulosa (por ejemplo, en una cantidad entre 2 % y 10 % como una solución acuosa); carboximetilcelulosa sódica (por ejemplo, en una cantidad entre 2 % y 10 % como una solución acuosa); etilcelulosa (por ejemplo, en una cantidad entre 5 % y 10 % como un alcohol o solución hidroalcohólica); poliacrilamidas (Polímero JR) (por ejemplo, en una cantidad entre 2 % y 8 % como una solución acuosa); poliviniloxoazolidona (Devlex) (por ejemplo, en una cantidad entre 5 % y 10 % como una solución acuosa o hidroalcohólica); y alcoholes polivinílicos (por ejemplo, en una cantidad entre 5 % y 20 % en soluciones acuosas). También se pueden usar otros adyuvantes para formar el núcleo de las micropartículas de las presentes realizaciones de la invención, cuyos ejemplos no limitantes incluyen: sulfato de calcio NF, fosfato dibásico de calcio NF, sulfato tribásico de calcio NF, almidón, carbonato de calcio, celulosa microcristalina, almidones modificados, lactosa, sacarosa y similares, Sta-Rx™, Avicel™, Solka-Floc™ BW40, ácido algínico, Explotab™, AUTOTAB™, goma guar, caolín Vecgum™ y bentonita. Estos adyuvantes se pueden usar hasta en 20 % p/p; y en ciertas realizaciones están presentes en una cantidad entre 3 % y 5 % p/p.

Como un ejemplo profético de estas realizaciones que tienen un núcleo que contiene bromhidrato de bupropion y un compuesto que es de sabor dulce, el bromhidrato de bupropion se puede granular usando el procedimiento siguiente: Se disuelve polivinilpirrolidona K-30 USP (240,0 g) en agua destilada (1.890,0 g) con agitación. Se colocan polvo de manitol USP (11.160 g) y bromhidrato de bupropion (600,0 g) en un granulador/procesador Zanchetta de 50 litros. Después de una mezcla en seco inicial de dos minutos de los polvos con la cortadora encendida y el propulsor ajustado a 200 rpm, la solución de polivinilpirrolidona K-30 se pulveriza lentamente en el lecho de mezcla del polvo usando un sistema de pulverización conducido por aire. El tiempo total de

granulación incluido el tiempo de adición de la solución es de aproximadamente ocho minutos. El punto final de granulación se determina visualmente y por la consistencia del material resultante. Después el material se descarga sobre bandejas y se seca a 80°C utilizando aire seco provisto durante un período de seis horas a un contenido de humedad de no más de 0,08 por ciento. El material seco se pasa luego a través 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 el recubrimiento combinados del bromhidrato de bupropion en micropartículas en las que el fármaco está localizado, al menos en parte, dentro del núcleo de la micropartícula pero es capaz de liberación inmediata. Para hacer esto, se mezclan en seco primero el bromhidrato de bupropion y un desintegrante granular; después se granula el polvo obtenido, en presencia de una mezcla de excipientes que comprenden al menos un aglutinante capaz de unir las partículas para dar granos; después los granos así formados se recubren pulverizándolos con una suspensión que comprende al menos un agente de recubrimiento y un desintegrante de membrana; y después los gránulos recubiertos obtenidos se secan. La distinción entre la granulación real y los pasos de recubrimiento es relativamente teórica, en la medida en que, aunque la función principal del aglutinante usado en el paso de granulación es unir las partículas, no obstante ya recubre parcialmente los granos formados. De la misma manera, aunque la función principal del agente de recubrimiento usado en el paso real de recubrimiento es completar 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 eligen del grupo que comprende los polímeros de celulosa y los polímeros acrílicos. Sin embargo, aunque el aglutinante y el agente de recubrimiento se eligen del mismo grupo de compuestos, difieren no obstante entre sí en su función como se mencionó previamente. Entre los polímeros de celulosa que se pueden elegir ventajosamente están etilcelulosa, hidroxipropilcelulosa (HPC), carboximetilcelulosa (CMC) e

hidroxipropilmetilcelulosa (HPMC) o sus mezclas. Entre los polímeros acrílicos que se pueden elegir ventajosamente están el copolímero de metacrilato de amonio (Eudragit® RL o RS), el poliacrilato (Eudragit® NE) y el copolímero de ácido metacrílico (Eudragit® L o S), siendo Eudragit® una marca registrada de Rohm. En al menos una realización, el aglutinante es de la misma naturaleza que el agente de recubrimiento. Para acelerar aún más la liberación del bromhidrato de bupropion, la suspensión de recubrimiento también comprende un permeabilizante que, debido a sus propiedades intrínsecas de solubilidad, causa perforación del recubrimiento de membrana, permitiendo así la liberación del bromhidrato de bupropion. Los ejemplos no limitantes de permeabilizantes incluyen povidona y sus derivados, polietilenglicol, sílice, polioles y polímeros de celulosa de viscosidad baja. Los polímeros del tipo de la hipromelosa, cuya viscosidad es igual a 6 centipoises, se usan, por ejemplo, como polímeros de celulosa de viscosidad baja. En al menos una realización, la mezcla en seco del polvo inicial y la granulación, el recubrimiento y los pasos de secado se realizan en un lecho fluidizado. En este caso, la mezcla del polvo inicial se fluidiza primero antes de ser granulada pulverizando dicho polvo con la mezcla de excipientes que comprende al menos un aglutinante, los granos obtenidos se recubren después por pulverización con la suspensión de recubrimiento, los gránulos recubiertos formados se secan finalmente en el lecho fluidizado. En al menos una realización, la mezcla de excipientes usada durante el paso de granulación y la suspensión de recubrimiento usada durante el paso de recubrimiento forman una única mezcla. En este caso, el paso de granulación se puede distinguir del paso de pulverización variando diferentes parámetros, como la velocidad de pulverización de la mezcla y la presión de pulverización de dicha mezcla. Por lo tanto, sólo algo de la mezcla de excipientes se usa durante el paso de granulación, mientras la otra porción se puede usar durante el paso de recubrimiento. Por lo tanto, la velocidad de pulverización de la suspensión de recubrimiento es mayor durante el paso de granulación que durante el paso de recubrimiento, mientras que la presión de pulverización de la suspensión de recubrimiento es menor durante el paso de granulación que durante el paso

de recubrimiento. En la práctica, 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 suspensión de recubrimiento está entre 10 g/minuto y 25 g/minuto y la presión de pulverización está entre 1 bar y 1,8 bar. Durante el paso de recubrimiento, la velocidad de pulverización de la suspensión de recubrimiento está entre 5 g/minuto y 15 g/minuto, mientras la presión de pulverización está entre 1,5 bar y 2,5 bar. En al menos una realización, entre 10 % y 20 % de la mezcla de excipientes se pulveriza durante el paso de granulación, el resto se pulveriza durante el paso de recubrimiento.

Como un ejemplo profético de estas realizaciones que implican la granulación y el recubrimiento combinados del bromhidrato de bupropion en micropartículas en las cuales el fármaco está ubicado al menos en parte dentro del núcleo de la micropartícula pero capaz de liberación inmediata, las micropartículas se pueden preparar según el proceso siguiente: Una solución de granulación se prepara primero disolviendo 48 g de etilcelulosa en 273 g de alcohol etílico. Una suspensión de recubrimiento se prepara después mezclando 97 g de etilcelulosa, 28,5 g de polietilenglicol 6000, 26 g de croscarmelosa de sodio, 10 g de sílice precipitado y 27,5 g de aspartamo en 1.900 g de alcohol etílico, hasta que se obtiene una suspensión homogénea. Después se fluidiza la mezcla de polvos que consiste en 700 g de bromhidrato de bupropion y 35 g de Acdisol. Después se comienza la granulación pulverizando la solución de granulación durante 15 a 20 minutos a una velocidad de pulverización de 25 g/minuto y una presión de pulverización de la suspensión 0,8 bar. El recubrimiento real se realiza después pulverizando la suspensión de recubrimiento durante 1 hora 30 minutos a una velocidad de pulverización de 15 a 20 g/minuto y una presión de pulverización de la suspensión de 1,5 bar.

Otras realizaciones de la invención implican el recubrimiento del material de bromhidrato de bupropion, formando de ese modo una micropartícula que contiene fármaco. Uno de dichos procesos para lograr esto implica:

(i) Mezclar y fluidizar una mezcla de polvo de principio activo y un adyuvante para obtener granos individuales,

(ii) Licuar por separado en condiciones de calor un agente de la matriz lipídica que comprende o un éster de ácido behénico y alcohol o un éster de ácido palmítico/esteárico y alcohol,

(iii) Recubrir la mezcla de polvos fluidizada en condiciones de calor pulverizando el agente de la matriz lipídica sobre los granos individuales,

(iv) Reducir la temperatura del producto combinado para permitir que el agente de la matriz lipídica solidifique.

Este proceso no requiere una fase de evaporación ni una fase de secado, ya que no requiere un paso de granulación por vía húmeda o en disolvente, haciendo posible así que esté libre de todo riesgo debido a la presencia de residuos tóxicos en el producto final. Además, no es necesario llevar a cabo la determinación cuantitativa de trazas de disolventes, un análisis que puede ser muy costoso. De acuerdo con el proceso de esta realización de la invención, las condiciones de pulverización y por lo tanto las características del recubrimiento se pueden modificar, para variar el perfil de liberación del bromhidrato de bupropion, variando varios parámetros, cuyas características de ajuste permanecen simples. Por lo tanto, la presión del aire de pulverización se puede aumentar para promover la formación de una película homogénea del agente de la matriz lipídica alrededor de los granos. De manera ventajosa, la velocidad de pulverización del agente de la matriz lípídica se puede reducir simultáneamente. En este caso, se obtiene el 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 fármaco. Por el contrario, la presión del aire de pulverización se puede reducir para promover la aglomeración de los granos unos con otros. De manera ventajosa, la velocidad de pulverización del agente de la matriz lipídica se puede aumentar simultáneamente. En este caso, se puede obtener un perfil de liberación de los granos obtenidos que es alto, correspondiente a una liberación rápida del bromhidrato de bupropion. En la práctica y de acuerdo con la masa de

polvo empleada, el valor de la velocidad de pulverización del agente de la matriz lipídica puede ser de dos a cuatro veces mayor cuando se desea promover la aglomeración de los granos unos con otros que cuando se desea promover la formación de una película homogénea alrededor de los granos. Por otro lado, el valor de la presión del aire de pulverización puede ser de una a dos veces menor cuando se desea promover la aglomeración de los granos unos con otros que cuando se desea promover la formación de una película homogénea alrededor de los granos. De acuerdo con el proceso para fabricar estas realizaciones, es posible, después de haber determinado un perfil de liberación del fármaco dado, variar los valores de la presión del aire de pulverización y de la velocidad de pulverización en toda la etapa de recubrimiento, haciendo posible promover la formación de una película homogénea alrededor de los granos o promover la aglomeración de los granos. Una vez que se ha determinado la secuencia de la duración de la presión del aire de pulverización y de la velocidad de pulverización, la operación de recubrimiento se puede llevar a cabo continuamente y automáticamente. De acuerdo con otra característica del proceso de fabricación de estas realizaciones, la temperatura de la mezcla del agente de la matriz licuado y del aire de pulverización es mayor en 35 °C a 60 °C que la temperatura de fusión del agente de la matriz lipídica. Asimismo, la temperatura del aire de fluidización y la del polvo es aproximadamente igual a la temperatura de fusión del agente de la matriz lipídica, más o menos 10°C. Además, para obtener una mezcla de los granos individuales, se puede usar un dispositivo de lecho fluidizado operado por aire o un dispositivo de turbina. Además, el agente de matríz lipídica se puede pulverizar mediante la técnica de pulverización de aire, es decir pulverización de líquido a presión en presencia de aire comprimido. De acuerdo con al menos una realización, se hace uso de un polvo que comprende el fármaco y el adyuvante. En otras palabras, después de mezclar y fluidizar los constituyentes combinados del polvo, el agente de la matríz lipídica se pulveriza sobre los granos individuales obtenidos. Para evitar la adhesión 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 sólo se trata una porción de los granos, se

inserta una etapa de lubricación de los granos entre la etapa de recubrimiento y la etapa de ponerlos en una forma farmacéutica. Además, para obtener mayor estabilidad de la composición farmacéutica, es decir para reducir al mínimo las modificaciones en relación con la liberación del bromhidrato de bupropion con el transcurso del tiempo, los gránulos o los comprimidos obtenidos en ciertas realizaciones de este ejemplo se pueden someter a una etapa de maduración en una estufa, durante al menos 8 horas, a una temperatura entre 45 °C y 60 °C; y en ciertas realizaciones a 55 °C.

Como un ejemplo profético de estas realizaciones de micropartículas que contienen fármaco que se forman recubriendo el material de bromhidrato de bupropion, las micropartículas que contienen fármaco se pueden preparar según el proceso siguiente: Se prepara una mezcla del polvo que comprende: bromhidrato de bupropion; fosfato dicálcico deshidratado; y polivinilpirrolidona. Los lotes de gránulos se preparan mediante un proceso que comprende 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 matríz lipídica (behenato de glicerilo, que se vende con el nombre comercial Compritol® 880 ATO) se licúa por separado a 120 °C; el agente de la matríz lipídica se pulveriza sobre la mezcla de polvos calentada, y, finalmente, la temperatura se reduce para permitir que el agente de la matríz lipídica solidifique. Estas etapas se llevan a cabo mientras se varían diversos parámetros, ya sea para promover la formación de una película homogénea alrededor de los granos o para promover la aglomeración de los granos, de conformidad con la tabla siguiente:

Parámetros	**Lote 1**	**Lote 2**	**Lote 3**	**Lote 4**
% en peso de la matriz lipídica				
Agente (Compritol® 888 ATO)	5	4	4	5
Velocidad de flujo de aire de fluidización (m^3/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 Compritol® (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 Compritol® (g/min)	41	20	40	40

Otra realización de la invención para recubrir el material de bromhidrato de bupropion, formando de ese modo una micropartícula que contiene fármaco, implica la formación de microcristales recubiertos que se pueden incorporar posteriormente en un comprimido. Mediante selección del polímero apropiado los microcristales pueden poseer características diversificadas como resistencia gástrica y liberación controlada debido al hecho de que dichos microcristales y microgránulos recubiertos o sin recubrir conserven, después de que se les haya dado forma de un comprimido multiparticulado, sus propiedades iniciales entre las cuales están incluidos el enmascaramiento del sabor, la resistencia gástrica y la liberación controlada del bromhidrato de bupropion. En ciertas realizaciones de este ejemplo, la lista no limitante de polímeros siguiente se puede seleccionar para el recubrimiento del bromhidrato de bupropion en el equipo de recubrimiento convencional basado en la fluidización: etilcelulosa (EC); hidroxipropilcelulosa (HPC); hidroxipropilmetilcelulosa (HPMC); gelatina; gelatina/acacia; gelatina/acacia/éter vinilmetílico-anhídrido maleico; gelatina/acacia/anhídrido etilenmaleico; carboximetilcelulosa; alcohol polivinílico; acetato ftalato de celulosa; nitrocelulosa; laca; cera; polímeros de polimetacrilato como Eudragit® RS; Eudragit® RL o

combinaciones de ambos, Eudragit® E y Eudragit NE30D; Kollicoat™ SR30D; y sus mezclas.

Micropartículas distribuidas en capas de fármaco

Las micropartículas distribuidas en capas de fármaco se pueden preparar recubriendo una partícula inerte o núcleo, como una esfera nonpareil (por ejemplo, una esfera de azúcar), con la sal de bupropion y un aglutinante polimérico. En ciertas realizaciones de las micropartículas distribuidas en capas de fármaco, los núcleos inertes incluyen materiales insolubles en agua como las esferas de celulosa o dióxido de silicio. En otras realizaciones, los núcleos inertes incluyen materiales solubles en agua como esferas de almidón, sal o azúcar. Los núcleos inertes pueden tener un diámetro que varía entre 100 micras y 2.000 micras. Por ejemplo, en ciertas realizaciones el diámetro de los núcleos inertes varía entre 150 micras y 1.500 micras. En al menos una realización, los núcleos inertes son esferas de azúcar NF, que contienen no menos de 62,5 % y no más de 91,5 % de sacarosa. En al menos una realización los núcleos inertes tienen densidad aparente sustancialmente uniforme, friabilidad baja y propiedades de generación de polvo bajas. En al menos una realización, los núcleos inertes se recubren con un sub recubrimiento osmótico que comprende un agente osmótico y un aglutinante polimérico. Además, los núcleos inertes se pueden recubrir inicialmente con un recubrimiento sellador para proporcionar una superficie del núcleo más uniforme y para reducir al mínimo cualquier efecto osmótico. La capa de recubrimiento sellador se puede aplicar al núcleo antes de la aplicación del fármaco, el aglutinante polimérico y todas las capas de película polimérica. En al menos una realización, la capa de recubrimiento sellador no modifica sustancialmente la liberación de la sal de bupropion. Los ejemplos de los materiales selladores adecuados que se pueden usar en el recubrimiento sellador incluyen agentes permeables o solubles como hidroxipropilmetilcelulosa, hidroxipropilcelulosa, etilcelulosa, un polímero polimetacrilato, hidroxipropiletilcelulosa, goma xantano y sus mezclas. En al menos una realización el sellador usado en el recubrimiento sellador es hidroxipropilmetilcelulosa. Se pueden agregar otros

agentes para mejorar la procesabilidad del sellador. Los ejemplos de dichos agentes incluyen talco, sílice coloidal, alcohol polivinílico, dióxido de titanio, sílice micronizado, sílice 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 suspensión usando un revestidor de lecho fluidizado (por ejemplo, recubrimiento de Wurster), o en un sistema de recubrimiento de paila. Los ejemplos de dichos recubrimientos selladores están comercialmente disponibles como los que se venden bajo las marcas comerciales Opadry® Blanco Y-1-7000 y Opadry® Blanco OY/B/28920, que son todos comercializados por Colorcon Limited, Inglaterra.

El aglutinante de estas realizaciones distribuidas en capas de fármaco se usa para adherir la capa de sal de bupropion al núcleo inerte o recubrimiento sellador del núcleo. En ciertas realizaciones, el aglutinante es soluble en agua, posee una adhesividad suficientemente alta para adherir la capa de sal de bupropion al núcleo inerte y posee una viscosidad apropiada para proporcionar una adhesión importante entre el núcleo inerte y la sal de bupropion. En otras realizaciones el aglutinante es insoluble en agua. En al menos una realización el aglutinante es etilcelulosa, un polímero de polimetacrilato, alcohol polivinílico, polivinilpirrolidona, copolímero de polivinilpirrolidona-acetato de vinilo (como Kollidon VA64), hidroxietilcelulosa, hidroxipropilmetilcelulosa de bajo peso molecular (por ejemplo, viscosidad de 1-50 cp a 20°C; 2-12 cp a 20°C; o 4-6 cp a 20°C), polimetacrilatos de hidroxipropilcelulosa o sus mezclas. Por ejemplo, en ciertas realizaciones la composición del aglutinante para el bromhidrato de bupropion es de 1 % a 25 % p/p; en otras realizaciones de 2 % a 10 % p/p; y aún en otras realizaciones de 3 % a 5 % p/p, expresada como un porcentaje del peso total del núcleo.

Se pueden usar disolventes para aplicar la sal de bupropion al núcleo inerte, cuyos ejemplos incluyen alcoholes inferiores como etanol, isopropanol y mezclas de alcohol/agua, acetona e hidrocarburos clorados.

Las micropartículas distribuidas en capas de fármaco se pueden preparar formando una suspensión o solución del aglutinante y la sal de bupropion y después distribuyendo en capas la suspensión o solución sobre el núcleo inerte o núcleo subrecubierto usando cualquiera de las técnicas de distribución en capas conocidas en el área, como recubrimiento en lecho fluidizado o recubrimiento en paila. Esto se puede efectuar en un único recubrimiento o el proceso se puede llevar a cabo en multiples capas, opcionalmente con pasos intervinientes de secado/evaporación. Este proceso se puede conducir de modo de producir micropartículas que contienen una cantidad deseada de sal de bupropion y lograr la dosificación y liberación deseadas con la administración in vivo.

En ciertas realizaciones, las micropartículas distribuidas en capas de fármaco se pueden preparar usando por ejemplo, el procedimiento del experimento hipotético siguiente: Se disuelven bromhidrato de bupropion (2,8 kg) e hidroxipropilmetilcelulosa (Methocel® E5) (0,40 kg) en una mezcla de agua y alcohol isopropílico. Después la solución de fármaco activo se puede pulverizar sobre las esferas de azúcar 30/35 (1,06 kg) en un procesador de lecho fluidizado con un separador de Wurster. Después las micropartículas del núcleo activo se pueden secar en un procesador de lecho fluidizado hasta que la pérdida por secado está por debajo de 1 %. Las micropartículas de bupropion se pueden pasar después a través de un tamiz de malla 16 y un tamiz de malla 30 y se pueden recoger micropartículas más pequeñas que una malla 16 y más grandes que una malla 30.

Recubrimientos que enmascaran el sabor de las micropartículas

Cada una de las micropartículas de la presente invención se puede recubrir con al menos un recubrimiento que enmascara el sabor. El recubrimiento que enmascara el sabor puede enmascarar el sabor del fármaco activo en las micropartículas. En al menos una realización las formulaciones de recubrimiento que enmascara el sabor contienen ingredientes poliméricos. Se contempla que se pueden usar en el recubrimiento otros excipientes

compatibles con los objetivos de la presente invención que enmascaran el sabor.

En al menos una realización, el recubrimiento que enmascara el sabor comprende un polímero como la etilcelulosa, que se puede usar como un polímero seco (como Ethocel®, Dow Corning) solubilizado en un disolvente orgánico antes de usar, o como una dispersión acuosa. Una dispersión acuosa comercialmente disponible de etilcelulosa es Aquacoat® (FMC Corp., Filadelfia, Pa., EE.UU.). El Aquacoat® se puede preparar disolviendo la etilcelulosa en un disolvente orgánico inmiscible con agua y luego emulsionar el mismo en agua en presencia de un tensioactivo y un estabilizador. Después de la homogeneización para generar gotitas submicrónicas, el disolvente orgánico se evapora al vacío para formar un pseudolátex. El plastificante no se incorpora en el pseudolátex durante la fase de fabricación. Por lo tanto, antes de usar el mismo como un recubrimiento, el Aquacoat se mezcla íntimamente con un plastificante adecuado antes de usar. Otra dispersión acuosa de etilcelulosa se comercializa como Surelease® (Colorcon, Inc., West Point, Pa., EE.UU.). Este producto se puede preparar incorporando un plastificante en la dispersión durante el proceso de fabricación. Se prepara una masa fundida caliente de un polímero, un plastificante (por ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, ácido oleico) como una mezcla homogénea, que luego se diluye con una solución alcalina para obtener una dispersión acuosa que se puede aplicar directamente sobre los sustratos.

En otras realizaciones, se pueden emplear polímeros acrílicos de polimetacrilato como polímeros que enmascaran el sabor. En al menos una realización, el recubrimiento que enmascara el sabor es una laca de resina acrílica usada en forma de una dispersión acuosa, como la que se obtiene comercialmente de Rohm Pharma con el nombre comercial Eudragit® o de BASF con el nombre comercial Kollicoat®. En otras realizaciones preferidas, el recubrimiento acrílico comprende una mezcla de dos lacas de resina acrílicas comercializadas por Rohm Pharma con el nombre comercial Eudragit® RL y Eudragit® RS, respectivamente.

Eudragit® RL y Eudragit® RS son copolímeros de ésteres acrílicos y metacrílicos con un contenido bajo de grupos amonio cuaternario, la relación molar entre los grupos amonio y los restantes ésteres (met)acrílicos neutros es de 1:20 en Eudragit® RL y 1:40 en Eudragit® RS. El peso molecular medio es 150.000. Las designaciones del código RL (permeabilidad alta) y RS (permeabilidad baja) se refieren a las propiedades de permeabilidad de estos agentes. Las mezclas Eudragit® RL/RS son insolubles en agua y en los líquidos digestivos. Sin embargo, los recubrimientos elaborados a partir de ellos son hinchables y permeables en soluciones acuosas y líquidos digestivos. Las dispersiones o soluciones de Eudragit® RL/SR de la presente invención se pueden mezclar en cualquier proporción deseada para obtener en último término un recubrimiento que enmascara el sabor con un perfil deseable de disolución del fármaco. Se pueden obtener formulaciones deseables, por ejemplo, a partir de un recubrimiento derivado de 100 % de Eudragit® RL; 50 % de Eudragit® RL con 50 % de Eudragit® RS; y 10 % de Eudragit® RL con 90 % de Eudragit® RS.

En otras realizaciones, el polímero que enmascara el sabor puede ser un polímero acrílico de carácter catiónico a base de metacrilato de dimetilaminoetilo y ésteres del ácido metacrílico neutros (como Eudragit® E, comercializados por Rohm Pharma). Los recubrimientos de polímero acrílico hidrofóbo de la presente invención pueden incluir además un copolímero neutro a base de poli(met)acrilatos, como Eudragit® NE (NE = éster neutro), comercializado por Rohm Pharma. Las películas de laca Eudragit® NE30D son insolubles en agua y líquidos digestivos, pero permeables e hinchables.

En otras realizaciones, el polímero que enmascara el sabor es una dispersión de poli(acrilato de etilo, metacrilato de metilo) 2:1 (Kollicoat® EMM 30 D, BASF).

En otras realizaciones, el polímero que enmascara el sabor puede ser un acetato polivinílico estabilizado con polivinilpirrolidona y lauril sulfato de sodio como Kollicoat® SR30D (BASF).

Otros polímeros que enmascaran el sabor incluyen hidroxipropilcelulosa (HPC); hidroxipropilmetilcelulosa (HPMC); hidroxietilcelulosa; gelatina; gelatina/acacia; gelatina/acacia/éter vinil metílico-anhídrido maleico; gelatina/acacia/anhídrido etilenmaleico; carboximetilcelulosa; alcohol polivinílico; nitrocelulosa; copolímeros injertados de alcohol polivinílico-polietilenglicol; laca; cera y sus mezclas.

Los recubrimientos que enmascaran el sabor se pueden aplicar a las micropartículas a partir de una o más soluciones o suspensiones de disolventes orgánicos o acuosos. En al menos una realización los disolventes orgánicos que se pueden usar para aplicar los recubrimientos que enmascaran el sabor incluyen uno o más entre acetona, alcoholes inferiores como etanol, isopropanol y mezclas alcohol/agua, hidrocarburos clorados y similares. Los dispositivos empleados para recubrir las micropartículas de la invención con un recubrimiento que enmascara el sabor incluyen los convencionalmente usados en el procesamiento farmacéutico, como los dispositivos de recubrimiento de lecho fluidizado. Los recubrimientos aplicados a las micropartículas pueden contener ingredientes diferentes de los polímeros funcionales. También se pueden usar uno o más 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 enmascara el sabor para influir en la velocidad de liberación del bromhidrato de bupropion desde la micropartícula. En otras realizaciones, no se incluye un formador de poros en el recubrimiento que enmascara el sabor. Los formadores de poros pueden ser inorgánicos u orgánicos e incluyen materiales como los materiales particulados que se pueden disolver, extraer o lixiviar del recubrimiento en el ambiente de uso. Después de la exposición a líquidos en el ambiente de uso, los formadores de poros se pueden, por ejemplo, disolver y se forman canales y poros que se llenan con el líquido ambiental.

Por ejemplo, los formadores de poros de ciertas realizaciones pueden comprender uno o más polímeros

hidrófilos solubles en agua para modificar las características de liberación de la formulación. Los ejemplos de los polímeros hidrófilos adecuados usados como formadores de poros incluyen hidroxipropilmetilcelulosa, éteres de celulosa y derivados proteicos de estos polímeros, los éteres de celulosa, especialmente hidroxialquilcelulosas y carboxialquilcelulosas. Además, se pueden usar polímeros solubles en agua sintéticos, cuyos ejemplos incluyen polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de polietileno, polidextrosa soluble en agua, sacáridos y polisacáridos, como pullulan, dextrano, sacarosa, glucosa, fructosa, manitol, lactosa, manosa, galactosa y sorbitol. En al menos una realización, el polímero hidrófilo comprende hidroxipropilmetilcelulosa.

Otros ejemplos no limitantes de formadores de poros 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 y citrato de sodio. Los sólidos formadores de poros también pueden ser polímeros solubles en el ambiente de uso, como los Carbowax™ y Carbopol™. Además, los formadores de poros abarcan dioles, polioles, alcoholes polihídricos, polialquilenglicoles, poliglicoles y poli(a-w)alquilendioles. Otros formadores de poros que pueden ser útiles en las formulaciones de la presente invención incluyen almidón, almidón modificado y derivados del almidón, gomas, incluidas, pero no exclusivamente, goma xantano, ácido algínico, otros alginatos, bentonita, veegum (silicato de aluminio y magnesio), agar, goma guar, goma de algarrobo, goma arábiga, quince psyllium, semilla de lino, goma de quimbombó, arabinogalactano, pectina, goma tragacanto, escleroglucano, dextrano, amilosa, amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de intercambio iónico, como polimetacrilato de potasio, carragenina, carragenina kappa, carragenina lambda, goma karaya, goma biosintética, etc. Otros formadores de poros incluyen materiales útiles para hacer láminas microporosas en los ambientes de uso, como policarbonatos compuestos de poliésteres lineales del ácido carbónico en los que los grupos carbonato reaparecen en la cadena polimérica, materiales microporosos como bisfenol, un

poli(cloruro de vinilo) microporoso, poliamidas microporosas, copolímeros modacrílicos microporosos, estireno-acrílico microporoso y sus copolímeros, polisulfonas porosas, poli(vinilideno) halogenado, policloroéteres, polímeros de acetal, poliésteres preparados por esterificación de un ácido dicarboxílico o anhídrido con un alquilenpoliol, poli(sulfuros de alquileno), fenólicos, poliésteres, polímeros porosos asimétricos, polímeros olefínicos reticulados, homopolímeros hidrófilos microporosos, copolímeros o interpolímeros con una menor densidad aparente y otros materiales similares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas), poli(benzimidazoles), colodión, proteínas regeneradas, poli(vinilpirrolidona) reticulada semisólida y sus mezclas.

En general, la cantidad de formador de poros incluida en los recubrimientos que enmascaran el sabor de ciertas realizaciones de la presente invención puede ser de 0,1 % a 80 %, en peso, en relación con el peso combinado del polímero y el formador de poros. Como el porcentaje de formador de poros se relaciona con el peso seco del polímero que enmascara el sabor, puede tener una influencia en las propiedades de liberación del fármaco desde la micropartícula 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 polímero que enmascara el sabor:formador de poros de 10:1 a 1:1. En ciertas realizaciones la relación de pesos secos de polímero que enmascara el sabor:formador de poros es de 8:1 a 1,5:1; y en otras realizaciones de 6:1 a 2:1. En al menos una realización que usa Eudragit® NE30D como polímero que enmascara el sabor y una hidroxipropilmetilcelulosa (viscosidad aprox. 5 cp (en una solución acuosa al 2 %)) como Methocel® E5, Pharmacoat 606G como el formador de poros soluble en agua, está presente una relación de pesos secos de polímero que enmascara el sabor:formador de poros de 2:1.

Los colorantes que se pueden usar en el recubrimiento que enmascara el sabor incluyen los colorantes (FD&C) de alimentos, fármacos y cosméticos, (D&C) de fármacos y

cosméticos o los colorantes externos (Ext. D&C) de fármacos y cosméticos. Estos colorantes son tinturas, lacas y ciertos colorantes naturales y derivados. Las lacas útiles incluyen tinturas absorbidas sobre hidróxido de aluminio u otros soportes adecuados.

Los saborizantes que se pueden usar en el recubrimiento que enmascara el sabor incluyen líquidos saborizantes naturales y sintéticos. Una lista ilustrativa de dichos saborizantes incluye aceites volátiles, aceites saborizantes sintéticos, compuestos aromáticos saborizantes, aceites, líquidos, oleorresinas y extractos derivados de plantas, hojas, flores, frutos, tallos y sus combinaciones. Una lista representativa, no limitante, de éstos incluye aceites cítricos, como de limón, naranja, toronja, lima y pomelo y esencias de frutas, incluidas manzana, pera, durazno, uva, frutilla, frambuesa, cereza, ciruela, ananás, albaricoque u otros saborizantes de fruta. Otros saborizantes útiles incluyen aldehídos y ésteres, como benzaldehído (cereza, almendra); citral, es decir, alfa citral (limón, lima); neral, es decir, beta citral (limón, lima); decanal (naranja, limón); aldehído C-8 (cítricos); aldehído C-9 (cítricos); aldehído C-12 (cítricos); tolil aldehído (cereza, almendra); 2,6-dimetiloctanal (fruto verde); 2-dodenal (mandarina); sus mezclas y similares.

Los edulcorantes que se pueden usar en el recubrimiento que enmascara el sabor incluyen glucosa (jarabe de maíz), dextrosa, azúcar invertido, fructosa y sus mezclas (cuando no se usa como un vehículo); sacarina y sus diversas sales, como la sal de sodio; dipéptidos edulcorantes como el aspartamo; compuestos dihidrochalcona, glicirricina; Steva Rebaudiana (estevióside); derivados clorados de sacarosa como sucralosa; y alcoholes de azúcares como sorbitol, manitol, xilitol y similares. También están contemplados los hidrolizados de almidón hidrogenados y los edulcorantes sintéticos como 3,6-dihidro-6-metil-1-1-1,2,3-oxatiazin-4-1-2,2-dióxido, en particular la sal de potasio (acesulfamo-K) 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 micropartícula también puede incluir uno o más excipientes farmacéuticamente aceptables como lubricantes, emulsionantes, antiespumantes, plastificantes, disolventes y similares.

Se pueden incluir lubricantes para ayudar a reducir la fricción de las micropartículas recubiertas durante la fabricación. Los lubricantes que se pueden usar en el recubrimiento que enmascara el sabor de la presente invención incluyen, pero no exclusivamente, ácido adípico, 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 fumarato de sodio, aceite mineral ligero, ésteres de ácidos graso como behenato de glicerilo, (es decir Compritol™), Stear-O-Wet™, Myvatex ™TL y sus mezclas. En al menos una realización, el lubricante se selecciona entre estearato de magnesio y talco. Las combinaciones de estos lubricantes son factibles. Cada lubricante puede estar presente en una cantidad entre 1 % y 100 % en peso del peso seco del polímero en el recubrimiento que enmascara el sabor. Por ejemplo, en ciertas realizaciones en las que el polímero que enmascara el sabor es Eudragit® NE30D o Eudragit® NE40D (Rohm America LLC) junto con un formador de poros hidrófilo, el lubricante está presente en una cantidad entre 1 % y 30 % en peso del peso seco del polímero; en otras realizaciones entre 2 % y 20 %; y aún en otras realizaciones en 10 % en peso del peso seco del recubrimiento que enmascara el sabor de la micropartícula. En otra realización en la que el polímero que enmascara el sabor es etilcelulosa (Ethocel™ polímero PR100, PR45, PR20, PR10 o PR7, o una mezcla), el lubricante puede estar presente en una cantidad entre 10 % y 100 % en peso del peso seco del recubrimiento que enmascara el sabor de la micropartícula; en otra realización entre 20 % y 80 %; y aún en otras realizaciones en 50 % en peso del peso seco del recubrimiento que enmascara el sabor de la

micropartícula. En otras realizaciones, el recubrimiento que enmascara el sabor no incluye un formador de poros.

Se pueden incluir uno o más emulsionantes (también denominados emulsificantes o emulgentes) en el recubrimiento que enmascara el sabor de la micropartícula para facilitar la emulsificación real durante la fabricación del recubrimiento y también para asegurar la estabilidad de la emulsión durante la vida útil en depósito del producto. Los emulsionantes útiles para el recubrimiento que enmascara el sabor de la micropartícula incluyen, pero no exclusivamente, materiales de origen natural y sus derivados semisintéticos, como los polisacáridos, así como ésteres de glicerol, éteres de celulosa, ésteres de sorbitán (por ejemplo, monooleato de sorbitán o Span™ 80) y polisorbatos (por ejemplo, Tween™ 80). Las combinaciones de emulsionantes son factibles. En al menos una realización, el emulsionante es Tween™ 80. El o los emulsionante(s) pueden estar presente en una cantidad entre 0,01 % y 5 % en peso del peso seco del polímero que enmascara el sabor de la micropartícula. Por ejemplo, en ciertas realizaciones el emulsionante está presente en una cantidad entre 0,05 % y 3 %; en otras realizaciones entre 0,08 % y 1,5 %, y aún en otras realizaciones en 0,1 % en peso del peso seco del polímero que enmascara el sabor de la micropartícula.

Se pueden incluir uno o más antiespumantes en el recubrimiento que enmascara el sabor de la micropartícula para reducir la producción de burbujas o de espuma durante la fabricación del recubrimiento. Los antiespumantes útiles para la composición del recubrimiento incluyen, pero no exclusivamente, simeticona, poliglicol, aceite de silicio y sus mezclas. En al menos una realización el antiespumante es Simeticona C. El antiespumante puede estar presente en una cantidad entre 0,1 % y 10 % del peso del recubrimiento que enmascara el sabor de la micropartícula. Por ejemplo, en ciertas realizaciones el antiespumante está presente en una cantidad entre 0,2 % y 5 %; en otras realizaciones entre 0,3 % y 1 %, y áun en otras realizaciones en 0,6 % en peso del peso seco del polímero que enmascara el sabor de la micropartícula.

Se pueden incluir uno o más plastificantes en el recubrimiento que enmascara el sabor de la micropartícula para proporcionar mayor flexibilidad y durabilidad durante la fabricación. Los plastificantes que se pueden usar en el recubrimiento que enmascara el sabor de la micropartícula incluyen monoglicéridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicérido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de colza, aceite de oliva, aceite de sésamo, citrato de trietilo; alcoholes polihídricos, glicerol, glicerina, sorbitol, ésteres 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 epoxidado, trimelitato de triisoctilo, ftalato de dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, 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, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de glicerol y sus mezclas. El plastificante puede estar presente en una cantidad entre 1 % y 80 % del peso seco del polímero que enmascara el sabor. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad entre 5 % y 50 %, en otras realizaciones entre 10 % y 40 % y aún en otras realizaciones en 20 % del peso seco del polímero que enmascara el sabor.

El recubrimiento que enmascara el sabor puede estar presente en una cantidad entre 1 % y 90 % en peso de la micropartícula, dependiendo de la elección del polímero, la relación polímero:formador de poros y el área superficial total de la formulación de la micropartícula. 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 polímero que enmascara el sabor usada

durante la fabricación está relacionada con el área superficial total del lote de micropartículas sin recubrir que requiere un recubrimiento. La cobertura del área superficial del polímero que enmascara el sabor puede variar de 0,5 mg/cm^2 a 20 mg/cm^2. Por ejemplo, en ciertas realizaciones la cobertura del área superficial del polímero que enmascara el sabor es de 0,6 mg/cm^2 a 10 mg/cm^2, y en otras realizaciones es de 1 mg/cm^2 a 5 mg/cm^2. En al menos una realización de la invención, se emplea Eudragit® E como el polímero que enmascara el sabor a una cobertura de área superficial de 4 mg/cm^2. Un enfoque para estimar el área superficial total de un lote multiparticulado es el método de permeabilidad según Blaine (ASTM Des. C 205-55), que se basa en el modelo matemático de flujo laminar a través de capilares dispuestos en paralelo.

A falta de una determinación exacta del área superficial total de una micropartícula, la cantidad de polímero que enmascara el sabor que se debe aplicar se puede expresar como un porcentaje de la micropartícula sin recubrir. Por ejemplo, en ciertas realizaciones el recubrimiento que enmascara el sabor está presente en una cantidad entre 5 % y 60 %; en otras realizaciones entre 10 % y 40 %; y aún en otras realizaciones entre 15 % y 35 % en peso de la micropartícula. En al menos una realización el recubrimiento que enmascara el sabor está presente en una cantidad de 30 % en peso de la micropartícula.

En ciertas realizaciones, el diámetro de las micropartículas (con o sin recubrimiento que enmascara el sabor) varía de 50 μm a 800 μm. Por ejemplo, en ciertas realizaciones el diámetro de las micropartículas varía de 100 μm a 600 μm y en otras realizaciones de 150 μm a 450 μm.

Recubrimiento de control de la liberación de la micropartícula

Cada una de las micropartículas de la presente invención se puede recubrir con al menos un recubrimiento de control de la liberación. Como se usa aquí, la expresión "recubrimiento de control de la liberación de la micropartícula" hace referencia al recubrimiento de control de la liberación que prácticamente rodea cada

micropartícula. El recubrimiento de control de la liberación de la micropartícula se diseña para lograr una liberación controlada de la sal de bupropion desde la micropartícula. Por ejemplo, el recubrimiento de control de la liberación de la micropartícula puede ser un recubrimiento entérico con baja solubilidad a un pH gástrico para reducir o minimizar la liberación del fármaco en la luz del estómago, al tiempo que posee una solubilidad dependiente del pH para facilitar la liberación del fármaco en el duodeno. En otra realización, el recubrimiento de control de la liberación puede ser un recubrimiento de liberación retardada que proporciona una liberación retardada de la sal de bupropion con un tiempo de retraso predeterminado que es independiente del pH del medio de disolución o alternativamente dependiente de dicho pH del medio de disolución. Por ejemplo, aumentando el espesor del recubrimiento de control de la liberación de la micropartícula usando un polímero de difusión independiente del pH se pueden lograr tiempos de retraso de 1 hora, 2 horas, 3 horas, 4 horas, 5 horas, 6 horas, 7 horas, 8 horas, 9 horas, 10 horas, 11 horas o 12 horas. Alternativamente, se pueden seleccionar polímeros de liberación controlada que se tornan solubles por encima de un determinado pH. La liberación del fármaco desde un sistema como ese se reduce o minimiza hasta que se excede el pH crítico para el polímero de elección. Con cualquiera de los enfoques, a continuación del retraso predeterminado, el fármaco se libera, por ejemplo en el transcurso de 1 hora para un impulso de liberación inmediata, o alternativamente durante un período prolongado, por ejemplo de 3 a 24 horas. En otras realizaciones, el recubrimiento de control de la liberación de la micropartícula puede proporcionar una barrera de difusión que es independiente del pH, facilitando así un perfil de liberación sostenida, produciéndose una liberación prácticamente total de la sal de bupropion entre 3 y 24 horas después de la administración. En al menos una realización, el recubrimiento de control de la liberación de la micropartícula proporciona una liberación retardada y sostenida de la sal de bupropion desde la micropartícula con una liberación prácticamente total en las 24 horas siguientes a la administración.

En ciertas realizaciones, el recubrimiento de control de la liberación de la micropartícula puede proporcionar una liberación prácticamente total de la sal de bupropion desde la micropartícula sin requerir el uso de ningún formador de poros. Los formadores de poros innecesarios que no son requeridos en el recubrimiento de control de la liberación de la micropartícula incluyen polímeros hidrófilos como hidroxipropilmetilcelulosa.

El recubrimiento de control de la liberación de la micropartícula incluye al menos un polímero en una cantidad suficiente para lograr una liberación controlada de la sal de bupropion. En al menos una realización de la invención el polímero con control de la liberación es un polímero acrílico. Los polímeros acrílicos adecuados incluyen, pero no exclusivamente, copolímeros del ácido acrílico y el ácido metacrílico, copolímeros de metacrilato de metilo, metacrilatos de etoxietilo, metacrilato de cianoetilo, copolímero de metacrilato de aminoalquilo, poli(ácido acrílico), poli(ácido metacrílico), copolímero de ácido metacrílico alquilamina, poli(metacrilato de metilo), poli(ácido metacrílico) (anhídrido), copolímeros de metacrilato de glicidilo y sus mezclas.

En al menos una realización el recubrimiento de control de la liberación comprende compuestos de amonio cuaternario polimerizables, cuyos ejemplos no limitantes incluyen ésteres aminoalquílicos y aminoalquilamidas cuaternizados del ácido acrílico y el ácido metacrílico, por ejemplo metosulfato de β-metacril-oxietil-trimetil-amonio, cloruro de β-acriloxi-propil-trimetil-amonio y metosulfato de trimetilaminometil-metacrilamida. El átomo de amonio cuaternario también puede formar parte de un heterociclo, como en el cloruro de metacriloxietilmetil-morfolinio o la correspondiente sal de piperidinio, o se puede unir a un grupo ácido acrílico o a un grupo ácido metacrílico a través de un grupo que contiene heteroátomos, como un grupo éter poliglicólico. Otros compuestos de amonio cuaternario polimerizables adecuados incluyen heterociclos de nitrógeno cuaternizados sustituidos con vinilo como las sales de metilvinil piridinio, los ésteres de vinilo de ácidos amino

carboxílicos cuaternizados y las sales de estiriltrialquilamonio. Otros compuestos de amonio cuaternario polimerizables útiles en la presente invención incluyen cloruro y metosulfato de acril- y metacril-oxietiltrimetilamonio, cloruro de bencildimetilamoniometil-metacrilato, metosulfato de dietilmetilamoniometil-acrilato y -metacrilato, cloruro de N-trimetilamoniopropilmetacrilamida y cloruro de N-trimetilamonio-2,2-dimetilpropil-1-metacrilato.

En al menos una realización, el polímero del recubrimiento de control de la liberación es un polímero acrílico compuesto de uno o más copolímeros de metacrilato de amonio. Los copolímeros de metacrilato de amonio (como los que se comercializan bajo la marca registrada Eudragit® RS y RL) se describen en el National Formulary (NF) XVII como copolímeros totalmente polimerizados de ésteres de ácido acrílico y metacrílico con un bajo contenido de grupos amonio cuaternario. Para obtener un perfil de disolución deseado para un principio terapéuticamente activo dado, como bromhidrato de bupropion, puede ser necesario en algunas realizaciones incorporar dos o más copolímeros de metacrilato de amonio con propiedades físicas diferentes. Por ejemplo, se sabe que cambiando la relación molar entre los grupos de amonio cuaternario y los ésteres (met)acrílicos neutros, se pueden modificar las propiedades de permeabilidad del recubrimiento de control de la liberación resultante.

En otras realizaciones de la presente invención, el recubrimiento de polímero acrílico incluye además un polímero cuya permeabilidad es dependiente del pH, como los polímeros aniónicos sintetizados a partir del ácido metacrílico y el éster metílico del ácido metacrílico. Dichos polímeros son comercializados, por ejemplo, por Rohm Pharma GmbH con el nombre comercial Eudragit® L y Eudragit® S y la relación entre los grupos carboxilo libres y los ésteres es 1:1 en Eudragit® L y 1:2 en Eudragit® S. Eudragit® L es insoluble en ácidos y agua pura, pero se torna cada vez más permeable por encima de pH 5,0. Eudragit® S es similar, excepto porque se torna cada vez más permeable por encima de pH 7. Los recubrimientos de polímero acrílico hidrófobo también pueden incluir un polímero con carácter catiónico a base

de metacrilato de dimetilaminoetilo y ésteres del ácido metacrílico neutros (como Eudragit® E, comercializado por Rohm Pharma). Los recubrimientos de polímero acrílico hidrofóbos de ciertas realizaciones pueden incluir además un copolímero neutro a base de poli(met)acrilatos, como Eudragit® NE (NE = éster neutro), comercializado por Rohm Pharma. Las películas de laca de Eudragit® NE 30D son insolubles en agua y líquidos digestivos, pero permeables e hinchables.

En otras realizaciones de la invención, el polímero con control de la liberación es una dispersión de poli(acrilato de etilo, metacrilato de metilo) 2:1 (Kollicoat® EMM 30 D, BASF). En otras realizaciones, el polímero con control de la liberación puede ser un acetato polivinílico estabilizado con polivinilpirrolidona y lauril sulfato de sodio como Kollicoat® SR30D (BASF). El perfil de disolución se puede alterar cambiando las cantidades relativas de diferentes lacas de resina acrílica incluidas en el recubrimiento. Asimismo, cambiando la relación molar entre el agente polimerizable que mejora la permeabilidad (por ejemplo, los compuestos de amonio cuaternario) en ciertas realizaciones y los ésteres (met)acrílicos neutros, se pueden modificar las propiedades de permeabilidad (y por lo tanto el perfil de disolución) del recubrimiento resultante.

En al menos una realización de la invención el polímero con control de la liberación es etilcelulosa, que se puede usar como un polímero seco (como Ethocel®, Dow Corning) solubilizado en disolvente orgánico antes de usar, o como una dispersión acuosa. Una dispersión acuosa comercialmente disponible de etilcelulosa es Aquacoat® (FMC Corp., Filadelfia, Pa., EE.UU.). El Aquacoat® se puede preparar disolviendo la etilcelulosa en un disolvente orgánico inmiscible con agua y luego emulsificar el mismo en agua en presencia de un tensioactivo y un estabilizador. Después de la homogeneización para generar gotitas submicrónicas, el disolvente orgánico se evapora al vacío para formar un pseudolátex. El plastificante no se incorpora en el pseudolátex durante la fase de fabricación. Por lo tanto, antes de usar el mismo como un recubrimiento, el

Aquacoat® se mezcla íntimamente con un plastificante adecuado antes de usar. Otra dispersión acuosa de etilcelulosa se comercializa como Surelease® (Colorcon, Inc., West Point, Pa., EE.UU.). Este producto se puede preparar incorporando un plastificante en la dispersión durante el proceso de fabricación. Se prepara una masa fundida caliente de un polímero, un plastificante (por ejemplo, sebacato de dibutilo) y un estabilizador (por ejemplo, ácido oleico) como una mezcla homogénea, que luego se diluye con una solución alcalina para obtener una dispersión acuosa que se puede aplicar directamente sobre los sustratos.

Otros ejemplos de polímeros que se pueden usar en el recubrimiento de control de la liberación de la micropartícula incluyen acetato ftalato de celulosa, acetato trimaleato de celulosa, ftalato de hidroxipropilmetilcelulosa, acetato ftalato de polivinilo, ftalato de alcohol polivinílico, laca; hidrogeles y materiales que forman geles, como polímeros carboxivinílicos, alginato de sodio, carmelosa de sodio, carmelosa de calcio, carboximetil almidón sódico, alcohol polivinílico, hidroxietilcelulosa, metilcelulosa, etilcelulosa, gelatina, almidón y polímeros reticulados a base de celulosa en los que el grado de reticulación es bajo para facilitar la adsorción de agua y la expansión de la matriz polimérica, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, almidón reticulado, celulosa microcristalina, quitina, pullulan, colágeno, caseína, agar, goma arábiga, carboximetilcelulosa sódica, (polímeros hidrófilos hinchables) poli(hidroxialquilmetacrilato) (peso molecular de 5 k a 5.000 k), polivinilpirrolidona (peso molecular de 10 k a 360 k), hidrogeles aniónicos y catiónicos, zeína, poliamidas, alcohol polivinílico con bajo contenido de acetato residual, una mezcla hinchable de agar y carboximetilcelulosa, copolímeros de anhídrido maleico y estireno, etileno, propileno o isobutileno, pectina (peso molecular 30 k a 300 k), polisacáridos como agar, goma acacia, goma karaya, goma tragacanto, alginas y goma guar, poliacrilamidas, óxidos de polietileno Polyox® (peso molecular de 100 k a 5.000 k), polímeros de acrilato AquaKeep®, diésteres de poliglucano, alcohol polivinílico y poli N-vinil-2-pirrolidona reticulados,

polímeros hidrófilos como los polisacáridos, metilcelulosa, carboximetilcelulosa de sodio o de calcio, hidroxipropilmetilcelulosa, hidroxipropilcelulosa, hidroxietilcelulosa, nitrocelulosa, carboximetilcelulosa, éteres de celulosa, metiletilcelulosa, etilhidroxietilcelulosa, acetato de celulosa, butirato de celulosa, propionato de celulosa, gelatina, almidón, maltodextrina, pullulan, polivinilpirrolidona, alcohol polivinílico, acetato de polivinilo, ésteres de ácidos grasos de glicerol, poliacrilamida, ácido poliacrílico, gomas naturales, lecitinas, pectina, alginatos, alginato de amonio, alginatos de sodio, calcio y potasio, alginato de propilenglicol, agar y gomas como arábiga, karaya, de algarrobo, tragacanto, carrageninas, guar, xantano, escleroglucano y sus mezclas y combinaciones.

En al menos una realización el recubrimiento de control de la liberación de las micropartículas comprende polímeros que pueden facilitar la adhesión a la mucosa del tubo digestivo. Ejemplos no limitantes de polímeros que se pueden usar para la adhesión a la mucosa incluyen carboximetilcelulosa, ácido poliacrílico, Carbopol™, Polycarbophil™, gelatina y otros polímeros naturales o sintéticos.

En al menos una realización las micropartículas se recubren con un recubrimiento de control de la liberación compuesto de:

(i) al menos un polímero formador de película que es insoluble en los líquidos del tubo digestivo, presente en una cantidad entre 50 % y 90 % (p. ej. entre 50 % y 80 %) en peso de la materia seca de la composición del recubrimiento de control de la liberación y que incluya al menos un derivado de celulosa no hidrosoluble, (p. ej. etilcelulosa, acetato de celulosa o sus mezclas);

(ii) al menos un polímero que contiene nitrógeno, presente en una cantidad entre 2 % y 25 % (p. ej. entre 5 % y 15 %) en peso de la materia seca de la composición del recubrimiento de control de la liberación y que incluya al menos una poliacrilamida, poli-N-vinilamida, poli-N-vinil-lactama, polivinilpirrolidina o sus mezclas;

(iii) opcionalmente al menos un plastificante presente en una cantidad entre 2 % y 20 % (p. ej. entre 4 % y 15 %) en peso de la materia seca de la composición del

recubrimiento de control de la liberación y que incluya al menos uno de los compuestos siguientes: ésteres, ftalatos, citratos y sebacatos de glicerol, ésteres de alcohol cetílico, aceite de ricino, cutina o sus mezclas; (iv) al menos un agente de superficie y/o un lubricante, presentes en una cantidad entre 2 % y 20 % (p. ej. entre 4 % y 15 %) en peso de la materia seca de la composición del recubrimiento de control de la liberación y que se eligen entre los tensioactivos aniónicos como las sales de ácidos grasos de metales alcalinos y alcalinotérreos, (p. ej. ácido esteárico, ácido oleico y sus mezclas), y/o entre los tensioactivos no iónicos como los ésteres polioxietilenados de sorbitán, derivados polioxietilenados de aceite de ricino, y/o entre los lubricantes como los estearatos (p. ej. estearatos de calcio, magnesio, aluminio, cinc y sus mezclas), estearilfumaratos (p. ej. estearilfumarato de sodio, behenato de glicerilo y sus mezclas); y mezclas de éstos; donde las micropartículas recubiertas se diseñan para ser capaces de permanecer en el intestino delgado durante un período de al menos 5 horas; en ciertas realizaciones al menos 7 horas; y en ciertas realizaciones durante un período entre 8 horas y 24 horas; de modo de permitir la absorción del bromhidrato de bupropion durante al menos parte de su tiempo en el intestino delgado.

En un ejemplo profético de esta realización de la invención, las micropartículas se recubren en un revestidor de lecho fluidizado con la solución de recubrimiento siguiente:

Eticelulosa	44,7 g
PVP	4,8 g
Aceite de ricino	4,8 g
Estearato de magnesio	6,1 g
Acetona	479 g
Isopranol	53 g

En otras realizaciones de la presente invención, la liberación del bromhidrato de bupropion desde una formulación de liberación controlada puede estar influida además, es decir, ajustada a una velocidad deseada, por la adición de uno o más formadores de poros al recubrimiento de control de la liberación, donde los

formadores de poros pueden ser inorgánicos u orgánicos y pueden incluir materiales que se pueden disolver, extraer o lixiviar del recubrimiento de control de la liberación en el ambiente de uso. Después de la exposición a líquidos en el ambiente de uso, los formadores de poros se disuelven, por ejemplo, y se forman canales y poros que se llenan con el líquido ambiental. Por ejemplo, los formadores de poros pueden incluir uno o más polímeros hidrófilos solubles en agua para modificar las características de liberación de la formulación. Los ejemplos no limitantes de polímeros hidrófilos adecuados incluyen hidroxipropilmetilcelulosa, éteres de celulosa y derivador proteicos de estos polímeros, éteres de celulosa, (p. ej. hidroxialquilcelulosas y carboxialquilcelulosas) y sus mezclas. Además, se pueden usar polímeros solubles en agua sintéticos, como polivinilpirrolidona, polivinilpirrolidona reticulada, óxido de polietileno, polidextrosa soluble en agua, sacáridos y polisacáridos, como pullulan, dextrano, sacarosa, glucosa, fructosa, manitol, lactosa, manosa, galactosa, sorbitol y sus mezclas. En al menos una realización, el o los polímeros hidrófilos comprenden hidroxipropilmetilcelulosa. Otros ejemplos de formadores de poros 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 formadores de poros también pueden ser polímeros que son solubles en el ambiente de uso, como los Carbowax®, Carbopol® y similares. Los formadores de poros abarcan dioles, polioles, alcoholes polihídricos, polialquilenglicoles, poliglicoles, poli(a-w)alquilendioles y sus mezclas. Otros formadores de poros que pueden ser útiles en las formulaciones de la presente invención incluyen almidón, almidón modificado y derivados del almidón, gomas, incluidas, pero no exclusivamente, goma xantano, ácido algínico, otros alginatos, bentonita, veegum (silicato de aluminio y magnesio), agar, goma guar, goma de algarrobo, goma arábiga, quince psyllium, semilla de lino, goma de quimbombó, arabinogalactano, pectina, goma tragacanto, escleroglucano, dextrano, amilosa, amilopectina, dextrina, etc., polivinilpirrolidona reticulada, resinas de intercambio iónico, como polimetacrilato de potasio,

carragenina, carragenina kappa, carragenina lambda, goma karaya, goma biosintética, y sus mezclas. Otros formadores de poros incluyen materiales útiles para hacer láminas microporosas en los ambientes de uso, como policarbonatos compuestos de poliésteres lineales del ácido carbónico en los que los grupos carbonato reaparecen en la cadena polimérica, materiales microporosos como bisfenol, un poli(cloruro de vinilo) microporoso, poliamidas microporosas, copolímeros modacrílicos microporosos, estireno-acrílico microporoso y sus copolímeros, polisulfonas porosas, poli(vinilideno) halogenado, policloroéteres, polímeros de acetal, poliésteres preparados por esterificación de un ácido dicarboxílico o anhídrido con un alquilenpoliol, poli(sulfuros de alquileno), fenólicos, poliésteres, polímeros porosos asimétricos, polímeros olefínicos reticulados, homopolímeros hidrófilos microporosos, copolímeros o interpolímeros con una menor densidad aparente y otros materiales similares, poli(uretano), poli(uretano) reticulado de cadena extendida, poli(imidas), poli(benzimidazoles), colodión, proteínas regeneradas, poli(vinilpirrolidona) reticulada semisólida y sus mezclas.

En otras realizaciones se puede incluir un tensioactivo o una base efervescente en el recubrimiento de control de la liberación, el cual puede reducir y en ciertas realizaciones vencer los efectos de tensión superficial. Además, el recubrimiento de control de la liberación de ciertas realizaciones puede incluir uno o más osmoagentes (es decir, que pueden liberar osmóticamente el principio activo desde el dispositivo proporcionando un gradiente de presión osmótica contra los líquidos externos), agentes de hinchamiento (es decir, los cuales pueden incluir, pero no exclusivamente, compuestos hidrófilos farmacéuticamente aceptables con diversas velocidades de hinchamiento en agua), u otros agentes farmacéuticamente aceptables (es decir, provistos en una cantidad suficiente para facilitar el ingreso de líquido ambiental sin causar la alteración del recubrimiento impermeable). Los tensioactivos que se pueden usar en el recubrimiento de control de la liberación de ciertas realizaciones pueden ser aniónicos, catiónicos, no iónicos o anfóteros. Los ejemplos no limitantes de dichos tensioactivos

incluyen lauril sulfato de sodio, dodecil sulfato de sodio, ésteres de sorbitán, polisorbatos, plurónicos, laurato de potasio y sus mezclas. Los ejemplos no limitantes de bases efervescentes que se pueden usar en el recubrimiento de control de la liberación de ciertas realizaciones incluyen sodio glicina carbonato, carbonato de sodio, carbonato de potasio, bicarbonato de sodio, bicarbonato de potasio, bicarbonato de calcio y sus mezclas. Los ejemplos no limitantes de osmoagentes que se pueden usar en el recubrimiento de control de la liberación de ciertas realizaciones incluyen cloruro de sodio, cloruro de calcio, lactato de calcio, sulfato de sodio, lactosa, glucosa, sacarosa, manitol, urea, otros compuestos orgánicos e inorgánicos conocidos en el área y sus mezclas. El agente de hinchamiento puede incluir, pero no exclusivamente, al menos un compuesto hidrófilo farmacéuticamente aceptable, con una tasa de hinchamiento o una cantidad de hinchamiento en agua a 25°C que es: mayor o igual que al menos 10 % en peso (p/p), mayor o igual que al menos 15 % en peso (p/p), o mayor o igual que al menos 20 % en peso (p/p). Los ejemplos no limitantes de agentes de hinchamiento que se pueden usar en el recubrimiento de control de la liberación de ciertas realizaciones de la presente invención incluyen polovinilpirrolidonas reticuladas (p. ej. poliplasdona, crospovidona y sus mezclas), carboxialquilcelulosas reticuladas, carboximetilcelulosa reticulada (p. ej. croscarmelosa sódica reticulada), polímeros hidrófilos de masa molar elevada (es decir, que pueden ser, pero no exclusivamente, mayores o iguales que 100.000 Daltons) los que pueden incluir, pero no exclusivamente: polivinilpirrolidona(s), óxidos de polialquileno (p. ej. óxido de polietileno, óxido de polipropileno y sus mezclas), hidroxialquilcelulosas (p. ej. hidroxipropilcelulosa, hidroxipropilmetilcelulosa y sus mezclas), carboxialquilcelulosa (p. ej. carboximetilcelulosa), almidón modificado (p. ej. glicolato de sodio), almidón o almidón natural (p. ej. de maíz, de trigo, de arroz, de papa y sus mezclas), celulosa (es decir que puede estar, pero no exclusivamente, en forma de polvo o en forma microcristalina), alginato de sodio, polacrilina potásica y sus correspondientes combinaciones o mezclas. En otras realizaciones, los ejemplos no limitantes de agentes de

hinchamiento incluyen los subconjuntos de compuestos siguientes: polovinilpirrolidona reticulada (p. ej. poliplasdona, crospovidona o sus mezclas), carboxialquilcelulosas reticuladas (p. ej., carboximetilcelulosas reticuladas como croscarmelosa sódica reticulada) y sus mezclas. En otras realizaciones, el agente de hinchamiento puede ser un polímero que contiene nitrógeno, cuyos ejemplos no limitantes pueden incluir polivinilpirrolidona, polivinilpirrolidona reticulada y sus mezclas. La concentración de agente de hinchamiento en el recubrimiento de control de la liberación de ciertas realizaciones de la presente invención puede estar entre 3 % y 40 % en peso de la micropartícula. Por ejemplo, en ciertas realizaciones la concentración del agente de hinchamiento en el recubrimiento de control de la liberación es de 4 % a 30 %, y en otras realizaciones de 5 % a 25 % en peso de la micropartícula.

En ciertas realizaciones se pueden usar, uno o más excipientes farmacéuticamente aceptables compatibles con los objetivos de la presente invención en el recubrimiento de control de la liberación, como un lubricante, un emulsionante, un antiespumante y/o un plastificante.

Se pueden incluir lubricantes en el recubrimiento de control de la liberación para ayudar a reducir la fricción de las micropartículas recubiertas durante la fabricación. Los lubricantes que se pueden usar en el recubrimiento de control de la liberación de ciertas realizaciones de la presente invención incluyen, pero no exclusivamente, ácido adípico, 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 fumarato de sodio, aceite mineral ligero, ésteres de ácidos grasos como behenato de glicerilo, (por ejemplo Compritol™), Stear-O-Wet™ y Myvatex ™ TL. En al menos una realización, el lubricante se selecciona entre estearato de magnesio, talco y sus mezclas. Las combinaciones de estos

lubricantes son factibles. Cada lubricante puede estar presente en una cantidad entre 1 % y 100 % en peso del peso seco del recubrimiento de control de la liberación. Por ejemplo, en ciertas realizaciones en las que el polímero con control de la liberación es Eudragit® NE30D o Eudragit® NE40D (Rohm America LLC) junto con un formador de poros hidrófilo, el lubricante está presente en una cantidad entre 1 % y 30 % en peso del peso seco del recubrimiento de control de la liberación; en otras realizaciones entre 2 % y 20 %; y aún en otras realizaciones en 10 % en peso del peso seco del recubrimiento de control de la liberación de la micropartícula. En otra realización en la que el polímero con control de la liberación es etilcelulosa (Ethocel™ polímero PR100, PR45, PR20, PR10 o PR7, o una mezcla), el lubricante puede estar presente en una cantidad entre 10 % y 100 % en peso del peso seco del recubrimiento de control de la liberación de la micropartícula; en otra realización entre 20 % y 80 %; y aún en otras realizaciones en 50 % en peso del peso seco del recubrimiento de control de la liberación de la micropartícula.

Se pueden incluir uno o más emulsionantes (también denominados emulsificantes o emulgentes) en el recubrimiento de control de la liberación de la micropartícula para facilitar la emulsificación real durante la fabricación del recubrimiento y también para asegurar la estabilidad de la emulsión durante la vida útil en depósito del producto. Los emulsionantes útiles para la composición del recubrimiento de control de la liberación de la micropartícula incluyen, pero no exclusivamente, materiales de origen natural y sus derivados semisintéticos, como los polisacáridos, así como ésteres de glicerol, éteres de celulosa, ésteres de sorbitán (por ejemplo, monooleato de sorbitán o Span™ 80) y polisorbatos (por ejemplo, Tween™ 80). Las combinaciones de emulsionantes son factibles. En al menos una realización, el emulsionante es Tween™ 80. El o los emulsionantes pueden estar presentes en una cantidad entre 0,01 % y 5 % en peso del peso seco del recubrimiento de control de la liberación de la micropartícula. Por ejemplo, en ciertas realizaciones el emulsionante está presente en una cantidad entre 0,05 % y

3 %; en otras realizaciones entre 0,08 % y 1,5 %, y aún en otras realizaciones en 0,1 % en peso del peso seco del recubrimiento de control de la liberación de la micropartícula.

Se pueden incluir uno o más antiespumantes en el recubrimiento de control de la liberación de la micropartícula para reducir la producción de burbujas o de espuma durante la fabricación del recubrimiento. Los antiespumantes útiles para la composición del recubrimiento incluyen, pero no exclusivamente, simeticona, poliglicol y aceite de silicio. En al menos una realización el antiespumante es Simeticona C. El antiespumante puede estar presente en una cantidad entre 0,1 % y 10 % del peso del recubrimiento de control de la liberación de la micropartícula. Por ejemplo, en ciertas realizaciones el antiespumante está presente en una cantidad entre 0,2 % y 5 %; en otras realizaciones entre 0,3 % y 1 %, y áun en otras realizaciones en 0,6 % en peso del peso seco del recubrimiento de control de la liberación de la micropartícula.

Se pueden incluir uno o más plastificantes en el recubrimiento de control de la liberación de la micropartícula para modificar las propiedades y características de los polímeros usados en el recubrimiento para un procesamiento conveniente durante la fabricación (por ejemplo para proporcionar mayor flexibilidad y durabilidad durante la fabricación). El término "plastificante" como se usa aquí incluye todos los compuestos capaces de plastificar o ablandar un polímero o un aglutinante usados en la presente invención. Una vez que se preparó el recubrimiento, ciertos plastificantes pueden actuar para aumentar la hidrofilicidad del recubrimiento en el ambiente de uso. Durante la fabricación del recubrimiento, el plastificante puede disminuir la temperatura de fusión o la temperatura de transición vítrea (temperatura del punto de ablandamiento) del polímero o aglutinante. La adición de un plastificante, como los PEG de bajo peso molecular, generalmente amplía el peso molecular promedio de un polímero en el cual está incluido disminuyendo de ese modo su temperatura de transición vítrea o punto de ablandamiento. Los plastificantes también pueden

generalmente reducir la viscosidad de un polímero. Los ejemplos no limitantes de plastificantes que se pueden usar en el recubrimiento de control de la liberación de la micropartícula incluyen monoglicéridos acetilados; acetil tributil citrato, butil ftalil butil glicolato; tartrato de dibutilo; ftalato de dietilo; ftalato de dimetilo; etil ftalil etil glicolato; glicerina; propilenglicol; triacetina; tripropioina; diacetina; ftalato de dibutilo; monoglicérido de acetilo; acetil trietil citrato, polietilenglicoles; aceite de ricino; aceite de colza, aceite de oliva, aceite de sésamo, citrato de trietilo; alcoholes polihídricos, glicerol, glicerina, sorbitol, ésteres 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 epoxidado, trimelitato de triisoctilo; ftalato de dietilhexilo, ftalato de di-n-octilo, ftalato de di-i-octilo, 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, fumarato de dietilo, succinato de dibutilo, malonato de dietilo, ftalato de dibutilo, sebacato de dibutilo, tributirato de glicerol y sus mezclas. El plastificante puede estar presente en una cantidad entre 1 % y 80 % del peso seco del recubrimiento de control de la liberación. Por ejemplo, en ciertas realizaciones el plastificante está presente en una cantidad entre 5 % y 50 %, en otras realizaciones entre 10 % y 40 % y aún en otras realizaciones en 20 % del peso seco del recubrimiento de control de la liberación.

El recubrimiento de control de la liberación puede estar presente en una cantidad entre 1 % y 100 % en peso de la micropartícula, dependiendo de la elección del polímero, la relación polímero:formador de poros y el área superficial total de la formulación de la micropartícula. Puesto que tiene que lograrse un cierto espesor del recubrimiento con conrol de la liberación para lograr el perfil de disolución deseado, la cantidad de recubrimiento de polímero requerida durante la fabricación está relacionada con el área superficial

total del lote de micropartículas sin recubrir que requiere un recubrimiento. La cobertura de área superficial del polímero con control de la liberación puede variar de 0,5 mg/cm^2 a 30 mg/cm^2. Por ejemplo, en ciertas realizaciones la cobertura de área superficial del polímero con control de la liberación es de 0,6 mg/cm^2 a 20 mg/cm^2, y en otras realizaciones es de 1 mg/cm^2 a 5 mg/cm^2. En al menos una realización de la invención, se emplea Eudragit® NE30D como el polímero con control de la liberación a una cobertura de área superficial de 10 mg/cm^2. Un enfoque para estimar el área superficial total de un lote multiparticulado es el método de permeabilidad según Blaine (ASTM Des. C 205-55), que se basa en el modelo matemático de flujo laminar a través de capilares dispuestos en paralelo. A falta de una determinación exacta del área superficial total de una micropartícula, la cantidad de polímero con control de la liberación que se debe aplicar se puede expresar como un porcentaje de la micropartícula sin recubrir.

El polímero con control de la liberación puede estar presente en una cantidad entre 1 % y 99 % en peso de la micropartícula recubierta, dependiendo del perfil de liberación controlada deseado. Por ejemplo, en ciertas realizaciones el polímero está presente en una cantidad entre 5 % y 80 %, y en otras realizaciones entre 10 % y 50 % en peso de la micropartícula recubierta. En al menos una realización en la que el polímero con control de la liberación es Eudragit® NE30D, Eudragit® NE40D (Rohm America LLC), Kollicoat® SR 30D, o una mezcla de éstos, el polímero está presente en una cantidad entre 1 % y 50 %; en otras realizaciones entre 5 % y 30 %; y aún en otras realizaciones en 15 % en peso de la micropartícula recubierta. En al menos una realización en la que el polímero con control de la liberación es etilcelulosa, el polímero está presente en una cantidad entre 1 % y 99 % en peso de la micropartícula recubierta; en otras realizaciones entre 5 % y 50 %; y aún en otras realizaciones en 20 % en peso de la micropartícula recubierta. En al menos una realización en la que el polímero con control de la liberación es Ethocel™, una etilcelulosa polímero grado PR100, PR45, PR20, PR10, PR7 o una mezcla de éstos, el polímero está presente en una cantidad entre 5 % y 30 % en peso de la micropartícula

recubierta; en otras realizaciones entre 10 % y 25 %; y aún en otras realizaciones en 20 % en peso de la micropartícula recubierta.

En ciertas realizaciones, el diámetro de las micropartículas (con o sin recubrimiento de control de la liberación) puede varíar de 50 μm a 800 μm. Por ejemplo, en ciertas realizaciones el diámetro de las micropartículas varía de 100 μm a 600 μm y en otras realizaciones de 150 μm a 450 μm.

Se contempla que en realizaciones alternativas, se pueden usar otros excipientes compatibles con los objetivos de la presente invención en el recubrimiento de control de la liberación de la micropartícula.

En al menos una realización, el recubrimiento de control de la liberación de la micropartícula incluye 96 % de Eudragit® NE30D, 1,9 % de estearato de magnesio, 1,9 % de talco, 0,04 % de Tween 80 y 0,19 % de Simeticona C, cuando se expresa como percentaje en peso de la composición del recubrimiento de control de la liberación seco. En otra realización, el recubrimiento de control de la liberación de la micropartícula incluye 68 % de etilcelulosa, 17 % de monoestearato de glicerilo y 15 % de acetil tributil citrato, cuando se expresa como percentaje en peso de la composición del recubrimiento de control de la liberación seco.

El proceso de fabricación del recubrimiento de control de la liberación de la micropartícula puede ser el siguiente. Se divide agua en dos porciones de 15 % y 85 %. Después se agregan el antiespumante y el emulsionante a la porción de 15 % de agua y se mezcla a 300 rpm para formar la porción A. En al menos una realización, el antiespumante es Simeticona C y el emulsionante es Tween™ 80. Después se agrega un primer lubricante a la porción 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. Después 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 realización, el segundo lubricante es estearato de magnesio. Finalmente,

se agrega una dispersión acuosa de un copolímero de un éster neutro y se mezcla durante 30 minutos a 500 rpm. En al menos una realización, la dispersión acuosa de un copolímero de un éster neutro es Eudragit® NE30D. La solución de recubrimiento de control de la liberación resultante se puede usar entonces para recubrir las micropartículas hasta un aumento de peso del 35 % con los parámetros siguientes: Una temperatura de entrada entre 10°C y 60°C, preferentemente entre 20 °C y 40°C, y más preferentemente entre 25°C y 35°C; una temperatura de salida entre 10°C y 60°C, preferentemente entre 20°C y 40°C, y más preferentemente entre 25°C y 35°C; una temperatura del producto entre 10°C y 60°C, preferentemente entre 15°C y 35°C, y más preferentemente entre 22°C y 27°C; un flujo de aire entre 10 m^3/h y 180 m^3/h, preferentemente entre 40 m^3/h y 120 m^3/h y más preferentemente entre 60 m^3/h y 80 m^3/h; y una presión de pulverización entre 0,5 bar y 4,5 bar, preferentemente entre 1 bar y 3 bar y más preferentemente de 2 bar. Las micropartículas resultantes recubiertas con el recubrimiento de control de la liberación se pueden descargar después desde la cámara de recubrimiento y curar en estufa con los parámetros siguientes: Una temperatura de curado entre 20°C y 65°C, preferentemente entre 30°C y 55°C y más preferentemente de 40°C; y un tiempo de curado entre 2 horas y 120 horas, preferentemente entre 10 horas y 40 horas y más preferentemente de 24 horas. También se puede usar cualquier otra tecnología que dé como resultado la formulación del recubrimiento de control de la liberación de la micropartícula compatible con los objetivos de la invención.

3.2.4 Formas farmacéuticas de micropartícula

Resultan formas farmacéuticas muy útiles cuando las micropartículas hechas de las composiciones que contienen una sal de bupropion, auxiliares de esferonización y otros excipientes se recubren con uno o más polímeros con control de la liberación. Las micropartículas con el recubrimiento de control de la liberación se pueden entonces combinar con una masa de excipientes y/o otros excipientes farmacéuticos y comprimir en forma de comprimidos. Los comprimidos convencionales se pueden fabricar comprimiendo las micropartículas recubiertas con

excipientes adecuados usando técnicas de compresión conocidas. El perfil de disolución de las micropartículas con recubrimiento de control de la liberación no es afectado de manera importante por la compresión de las micropartículas en forma de comprimidos. Las formas farmacéuticas resultantes se benefician de la facilidad de procesamiento asociada con el uso de masas de excipientes y de las propiedades de liberación asociadas con micropartículas con un recubrimiento de control de la liberación. Alternativamente, con las micropartículas recubiertas se pueden llenar cápsulas.

Las formas de administración de acuerdo con la invención son adecuadas para la administración oral. En ciertas realizaciones las formas de administración son comprimidos y cápsulas. No obstante, la composición de la invención también puede tomar la forma de pelets, perlas o microcomprimidos, que después se pueden colocar en cápsulas o comprimir en una forma farmacéutica sólida unitaria. Los técnicos con experiencia pueden preparar otras formas farmacéuticas sólidas orales como las divulgadas aquí, a pesar del hecho de que dichas formas farmacéuticas sólidas orales pueden ser más difíciles de fabricar con fines comerciales.

La presente invención también contempla combinaciones de micropartículas recubiertas de manera diferente para dar una forma farmacéutica a fin de ofrecer una diversidad de perfiles de liberación distintos. Por ejemplo, en ciertas realizaciones, se pueden combinar micropartículas con un perfil de liberación retardada con otras micropartículas que tienen un perfil de liberación sostenida para proporcionar una formulación de bupropion de liberación controlada de múltiples componentes. Además, otras realizaciones pueden incluir uno o más componentes adicionales de liberación inmediata de bupropion. El componente de liberación inmediata de bupropion puede tomar la forma de micropartículas de bupropion sin recubrir o polvos; también son conocidas por los técnicos las micropartículas de bupropion recubiertas con un recubrimiento de liberación inmediata muy soluble, como un recubrimiento tipo Opadry®, o una combinación de cualquiera de los anteriores. Después los múltiples componentes se pueden mezclar juntos en la relación

deseada y colocar en una cápsula o preparar como comprimidos. Los ejemplos de formulaciones de bupropion de liberación controlada de múltiples componentes se describen en US 6,905,708.

3.2.5 Tecnología de sorbición de la dosis

La presente invención también contempla un sistema de administración oral para liberar micropartículas que contienen bromhidrato de bupropion mezcladas con un líquido. Por ejemplo, se proporciona un sistema de administración oral que comprende una cámara de la formulación del fármaco hueca. En al menos una realización, la cámara tiene un primer y un segundo extremos y contiene una formulación en forma de micropartículas. En al menos una realización, la formulación de fármaco comprende bromhidrato de bupropion. El sistema comprende además un líquido que pasa por el retenedor de la formulación del fármaco en el primer extremo de la cámara. El retenedor evita la liberación de las micropartículas desde el primer extremo permitiendo la entrada de líquido a la cámara. En otras realizaciones, las micropartículas contenidas dentro de la cámara comprenden bromhidrato de bupropion y al menos otro fármaco.

La presente invención proporciona además un método para la administración por vía oral de las micropartículas que contienen la formulación de bromhidrato de bupropion mezclada con un líquido. El método implica la introducción de micropartículas de la formulación de bromhidrato de bupropion en una cámara de administración del fármaco hueca de un dispositivo de administración de fármacos. La cámara tiene un primer extremo y un segundo extremo. El primer extremo de la cámara tiene un líquido que pasa por el retenedor de la formulación del fármaco. El dispositivo de administración del fármaco tiene un primer y un segundo extremos. El primer extremo del dispositivo de administración del fármaco se introduce en un líquido y el segundo extremo se introduce en la boca de un paciente. Después el paciente aplica succión al segundo extremo del dispositivo para provocar la administración del líquido y las micropartículas de la formulación de bromhidrato de bupropion en la boca del paciente.

El término "retenedor de la formulación del fármaco" como se usa aquí, se refiere a una válvula, obturador o restricción o similares que evita el pasaje de la formulación del fármaco desde el dispositivo. Por "líquido que pasa por el retenedor de la formulación del fármaco" se concibe una válvula, obturador o restricción o similar que permite el pasaje de líquidos pero no permite el pasaje de otros ingredientes como la formulación del fármaco que está contenida en el dispositivo de administración.

El dispositivo dispensador de esta realización de la invención tiene uso cuando es inconveniente o inseguro usar formas farmacéuticas orales sólidas como cápsulas o comprimidos. Los dispositivos pueden ser particularmente útiles en las poblaciones de pacientes geriátricas o pediátricas pero también pueden ser útiles para los que tienen dificultad para tragar cápsulas o comprimidos. Durante un programa terapéutico, se puede administrar al paciente un único dispositivo de administración o varios dispositivos.

En general el dispositivo está en la forma preparada antes de la colocación en un líquido. En al menos una realización el dispositivo dispensador comprende una cámara de formulación del fármaco hueca con un primer extremo y un segundo extremo. Contenidos dentro de la cámara se encuentran la formulación del fármaco y el líquido que pasa por el retenedor de la formulación del fármaco. El líquido que pasa por el retenedor de la formulación del fármaco comprende una restricción y un obturador unidireccional. El diámetro de la abertura es más pequeño que el obturador. En al menos una realización la restricción se hace plegando un extremo de la cámara. El segundo extremo de la cámara tiene un retenedor de la formulación del fármaco para evitar la liberación del obturador. En al menos una realización el retenedor se prepara plegando el extremo de la cámara. Después las micropartículas de bromhidrato de bupropion se colocan en la cámara. Se coloca una tapa sobre el segundo extremo de la cámara antes de usar para evitar la liberación de la formulación del fármaco. En la forma preparada, el obturador prácticamente sella el primer extremo de la

cámara, evitando de ese modo la pérdida de la formulación del fármaco por el primer extremo.

El dispositivo se puede elaborar de cualquier material adecuado que sea física y/o químicamente compatible tanto con el fármaco activo como con el diluyente líquido que se va a mezclar allí. En ciertas realizaciones, los materiales representativos para elaborar dispositivos incluida la cámara de la formulación del fármaco, el miembro tubular alargado, las tapas y las lengüetas, incluyen, sin limitación, papel, plástico como copolímeros de propileno/estireno, polipropileno, polietileno de alta densidad, polietileno de baja densidad y similares. Los dispositivos pueden tener un diámetro interno entre 3 mm y 8 mm y un espesor de pared entre 0,1 mm y 0,4 mm. Los dispositivos pueden tener entre 10 cm y 30 cm de longitud.

El líquido que pasa por el retenedor de la formulación del fármaco permite el flujo libre de medio líquido pero prohíbe el pasaje de la formulación del fármaco desde el dispositivo antes de la administración. Donde el retenedor comprende un obturador unidireccional o válvula, el obturador o la válvula sellarán la paja a la presión atmosférica. Cuando se aplica succión, el líquido se hace llegar alrededor del obturador y dentro de la cámara de la formulación del fármaco. Además, el obturador tiene una densidad de menos de uno de modo que ascenderá a la parte superior a medida que la formulación del fármaco se administra en la cavidad bucal. Cuando ya no se aplique succión, el obturador quedará en la posición más alta que alcanzó durante la sorbición. El obturador se puede preparar de espuma de polietileno de celda cerrada como EthaFoam®. Otras formas de obturador unidireccional pueden ser un globo del material elastomérico, una válvula de bola mecánica unidireccional y similares.

Los ejemplos de líquido que se pueden usar para suspender la formulación del fármaco sorbiendo a través de la cámara de formulación del fármaco incluye cualquier líquido de sabor agradable como agua, jugo, leche, soda, café, té, etc. Se debe tener cuidado de asegurar la

compatibilidad del líquido con la formulación del fármaco.

En al menos una realización, un dispositivo de administración por sorbición de la dosis de acuerdo con la presente invención se puede preparar del modo siguiente. Se termosellan pajas de tamaño Jumbo con un diámetro interno de 0,21 pulgadas y una longitud de 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 cápsula de gelatina dura. Después se colocan las micropartículas dentro del extremo abierto de la paja. Se recorta un obturador "unidireccional" hecho de espuma de polietileno de celdas cerradas, Microfoam® (DuPont) para que se ajuste convenientemente dentro de la paja. Después el obturador se coloca dentro de la paja, encima de las micropartículas. Durante la operación, el extremo del obturador de la paja se coloca en un vaso de agua y se retira la cápsula de gelatina protectora de la parte superior de la paja. Al aplicar succión lentamente a través del extremo parcialmente sellado de la paja, las micropartículas se succionan en la boca y se tragan fácilmente.

Formas farmacéuticas osmóticas

Las formas farmacéuticas osmóticas, los dispositivos de administración osmótica, las formas farmacéuticas osmóticas de liberación modificada o los sistemas de liberación extendida controlada por ósmosis son términos usados aquí indistintamente y se definen para significar formas farmacéuticas que dispensan forzadamente la sal de bupropion por la presión creada por ósmosis o por ósmosis y difusión del líquido en un material que se expande y fuerza que la sal de bupropion se dispense desde la forma farmacéutica osmótica. La ósmosis se puede definir como el flujo de disolvente de un compartimiento con una concentración baja del soluto a un compartimiento con una concentración alta del soluto. Los dos compartimientos están separados por una membrana, pared o recubrimiento, que permite el flujo del disolvente (un líquido, medio acuoso, o líquidos biológicos) pero no del soluto. Los ejemplos de dichas membranas pueden ser por ejemplo, una membrana semipermeable, microporosa, membrana asimétrica,

donde la membrana asimétrica puede ser permeable, semipermeable, perforada o no perforada y puede administrar la sal de bupropion mediante bombeo osmótico, difusión o los mecanismos combinados de difusión y bombeo osmótico. Por lo tanto, en principio, la liberación controlada por ósmosis de la sal de bupropion implica el transporte osmótico de un medio acuoso al interior de la forma farmacéutica osmótica seguido de la disolución de la sal de bupropion y el transporte posterior de la solución saturada de la sal de bupropion mediante bombeo osmótico de la solución a través de al menos un pasadizo en la membrana semipermeable o mediante una combinación de ósmosis y difusión a través de la membrana semipermeable.

Es bien sabido por los técnicos con experiencia que la velocidad de liberación deseada in vitro y los parámetros farmacocinéticos in vivo pueden ser influidos por varios factores, como por ejemplo, la cantidad de sal de bupropion usada para formar el núcleo, la cantidad de excipiente farmacéuticamente aceptable usado para formar el núcleo, el tipo de excipiente farmacéuticamente aceptable usado para formar el núcleo, la cantidad o el tipo de otros materiales usados para formar el núcleo como, por ejemplo, osmoagentes (las expresiones osmoagente, solutos osmóticamente eficaces, compuesto osmóticamente eficaz y agentes osmóticos se usan aquí indistintamente) osmopolímeros y cualquier combinación de éstos. El perfil de liberación también puede ser influido por el material usado para formar la membrana semipermeable que cubre el núcleo o por el material usado para formar cualquier recubrimiento, como un recubrimiento de control de la liberación (por ejemplo, un recubrimiento que enlentece la liberación) sobre la membrana semipermeable. Con estos factores en mente, se puede diseñar por consiguiente un dispositivo osmótico para que presente una velocidad de liberación in vitro tal que en ciertas realizaciones, después de 2 horas se libere de 0 a 20 % en peso de la sal de bupropion, después de 4 horas se libere de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libere de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libere más de 80 % en peso de la sal de bupropion, cuando se mide por ejemplo usando un aparato

tipo 1 de la USP (Método de cesta rotatoria) en 900 ml de agua, HCl 0,1 N, HCl 0,1 N + Cetrimida al 0,1 %, solución amortiguadora USP de pH 1,5, solución amortiguadora de acetato de pH 4,5, solución amortiguadora de fosfato de pH 6,5 o solución amortiguadora de fosfato de pH 7,4 a 75 rpm a 37°C ± 0,5°C. Alternativamente la disolución se puede efectuar en los medios USP-3 como LGS de pH 1,2, solución amortiguadora de acetato de pH 4,5 o solución amortiguadora de fosfato de pH 6,8.

También se pueden diseñar dispositivos osmóticos para lograr una liberación in vitro de no más de 40 % después de 2 horas, una liberación de 40 % a 75 % después de 4 horas, al menos una liberación de 75 % después de 8 horas y al menos una liberación de 85 % después de 16 horas cuando se analiza usando un medio de disolución como el identificado antes o conocido en el área.

En ciertas realizaciones de la presente invención, se proporciona una forma farmacéutica osmótica que tiene un núcleo que comprende la sal de bupropion y uno o más excipientes. En al menos una realización la forma farmacéutica osmótica comprende un osmoagente. El sistema de administración osmótica por ejemplo, puede estar en forma de un comprimido o una cápsula que contiene micropartículas.

En ciertas realizaciones, el núcleo de la forma farmacéutica osmótica comprende un polímero hinchable en agua, cuyos ejemplos no limitantes incluyen hidroxipropilcelulosa, alquilcelulosa, hidroxialquilcelulosa, óxido de polialquileno, óxido de polietileno y sus mezclas. Se puede incluir un aglutinante en el núcleo de ciertas realizaciones de la forma farmacéutica osmótica para aumentar la fuerza mecánica del núcleo. Los ejemplos no limitantes de aglutinantes incluyen polivinilpirrolidona, polímero carboxivinílico, metilcelulosa, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, un polímero de óxido de polietileno de bajo peso molecular, hidroxipropilmetilcelulosa, dextrina, maltodextrina, gelatina, alcohol polivinílico, goma xantano, carbómeros, carragenina, derivados del almidón y sus mezclas. Se pueden incluir lubricantes en ciertas realizaciones de la

forma farmacéutica osmótica 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 ácido esteárico, estearato de 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 invención en el núcleo de la forma farmacéutica osmótica para facilitar la preparación y/o mejorar la aceptabilidad por el paciente de la forma farmacéutica osmótica final según se describe aquí. Los excipientes inertes adecuados son bien conocidos por los técnicos con experiencia y se pueden encontrar en la bibliografía pertinente, por ejemplo en el Handbook of Pharmaceutical Excipients (Rowe et al., 4ª Ed., Pharmaceutical Press, 2003).

En al menos una realización, la presente invención comprende una forma farmacéutica osmótica de liberación modificada que comprende bromhidrato de bupropion presente en una cantidad terapéuticamente eficaz, la cual libera el bromhidrato de bupropion dispensando forzadamente el bromhidrato de bupropion desde el núcleo a través de una membrana semipermeable mediante difusión y/o a través de al menos un pasadizo en la membrana por bombeo osmótico (i) todo o en parte mediante la presión creada en el núcleo por ósmosis, es decir, presión hidrostática positiva de un líquido, disolvente, líquido biológico o medios acuosos y/o todo o en parte por expansión de un material hinchable que fuerza la dispensación del bromhidrato de bupropion desde el núcleo de la forma farmacéutica, y (ii) se formula de tal manera que la forma farmacéutica presenta una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion.

En al menos una realización, la forma farmacéutica de liberación modificada comprende un dispositivo de

administración osmótica que comprende un núcleo sólido homogéneo que contiene fundamentalmente la sal de bupropion presente en una cantidad terapéuticamente eficaz con al menos un excipiente farmacéuticamente aceptable, donde dicho núcleo está rodeado por una membrana semipermeable que permite el ingreso de un líquido acuoso en el núcleo y la salida de la sal de bupropion desde el núcleo hacia el exterior de la forma farmacéutica a través de al menos un pasadizo o mediante una combinación de ósmosis y difusión de tal manera que la forma farmacéutica presenta una velocidad de liberación in vitro tal que después de 2 horas, se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion, y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion, o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende una forma farmacéutica multiparticulada, en la que cada micropartícula comprende un dispositivo de administración osmótica, donde cada micropartícula comprende un núcleo sólido homogéneo que contiene fundamentalmente la sal de bupropion con al menos un excipiente farmacéuticamente aceptable, donde dicho núcleo de cada micropartícula está rodeado por una membrana semipermeable que permite el ingreso de un líquido acuoso en el núcleo y la salida de la sal de bupropion desde el núcleo hacia el exterior de la forma farmacéutica a través de numerosos poros formados en la membrana semipermeable por inclusión de un formador de poros en la membrana o por combinación de ósmosis y difusión para permitir la comunicación del núcleo con el exterior del dispositivo para la administración de la sal de bupropion y se formula de manera tal que la forma farmacéutica comprende una cantidad terapéuticamente eficaz de la sal de bupropion y presenta una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de

bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende una forma farmacéutica multiparticulada, en la que cada micropartícula comprende un dispositivo de administración osmótica, donde cada micropartícula comprende un núcleo sólido homogéneo que contiene fundamentalmente la sal de bupropion mezclada con al menos un excipiente farmacéuticamente aceptable, un osmoagente y/o un osmopolímero, donde dicho núcleo de cada micropartícula está rodeado por una membrana semipermeable que permite el ingreso de un líquido acuoso en el núcleo y la salida de la sal de bupropion desde el núcleo hacia el exterior de la forma farmacéutica a través de numerosos poros formados en la membrana semipermeable por inclusión de un formador de poros en la membrana o por combinación de ósmosis y difusión para permitir la comunicación del núcleo con el exterior del dispositivo de administración de la sal de bupropion y se formula de manera tal que la forma farmacéutica contenga una cantidad terapéuticamente eficaz de la sal de bupropion y presente una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende una forma farmacéutica multiparticulada, en la que cada micropartícula comprende un núcleo sólido homogéneo que contiene fundamentalmente la sal de bupropion con al menos un excipiente farmacéuticamente aceptable mezclado con un osmoagente

y/o un osmopolímero y/o un potenciador de la absorción, donde dichas micropartículas se comprimen en forma de un comprimido junto con al menos un excipiente farmacéuticamente aceptable, donde dicho comprimido está rodeado por una membrana semipermeable que permite el ingreso de un líquido acuoso en el núcleo y la salida de la sal de bupropion desde el interior del comprimido hacia el exterior de la forma farmacéutica a través de al menos un pasadizo en la membrana semipermeable y/o por difusión a través de la membrana semipermeable para permitir la comunicación del interior del comprimido con el exterior del comprimido para la administración de la sal de bupropion y se formula de manera tal que la forma farmacéutica contenga una cantidad terapéuticamente eficaz de la sal de bupropion y presente una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende una forma farmacéutica multiparticulada, en la que cada micropartícula contiene una esfera de azúcar o una perla sin color recubierta con al menos una capa que contiene fundamentalmente la sal de bupropion con al menos un excipiente farmacéuticamente aceptable, donde dicha al menos una capa está rodeada por una membrana semipermeable que permite el ingreso de un líquido acuoso en la capa y la salida de la sal de bupropion desde la capa hacia el exterior de la forma farmacéutica a través de numerosos poros formados en la membrana semipermeable por inclusión de un formador de poros en la membrana y/o por difusión para permitir la comunicación del núcleo con el exterior del dispositivo para la administración de la sal de bupropion y se formula de manera que la forma farmacéutica contenga una cantidad terapéuticamente eficaz de la sal de bupropion y presente una velocidad de liberación in vitro tal que

después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende una forma farmacéutica multiparticulada, en la que cada micropartícula comprende una esfera de azúcar o una perla sin color recubierta con al menos una capa que contiene fundamentalmente la sal de bupropion mezclada con al menos un excipiente farmacéuticamente aceptable, un osmoagente y/o un osmopolímero, donde dicha al menos una capa está rodeada por una membrana semipermeable que permite el ingreso de un líquido acuoso en la capa y la salida de la sal de bupropion desde la capa hacia el exterior de la forma farmacéutica a través de numerosos poros formados en la membrana semipermeable por inclusión de un formador de poros en la membrana y/o por difusión para permitir la comunicación del núcleo con el exterior del dispositivo para la administración de la sal de bupropion y se formula de manera tal que la forma farmacéutica contenga una cantidad terapéuticamente eficaz de la sal de bupropion y presente una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende una forma farmacéutica osmótica de liberación modificada que comprende un núcleo homogéneo que contiene una cantidad terapéuticamente eficaz de la sal de bupropion mezclada con un osmoagente

y/o un osmopolímero y/o un potenciador de la absorción, donde dicho núcleo está rodeado por una pared atóxica, membrana o recubrimiento, como por ejemplo una membrana semipermeable que permite la entrada de un líquido acuoso en el núcleo y la salida de la sal de bupropion desde el núcleo hacia el exterior de la forma farmacéutica a través de al menos un pasadizo en la membrana semipermeable y/o por difusión a través de la membrana para permitir la comunicación del núcleo con el exterior de la forma farmacéutica para la administración de la sal de bupropion y se formula de manera tal que la forma farmacéutica presente una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende un dispositivo de administración osmótica que contiene la sal de bupropion presente en una cantidad terapéuticamente eficaz en una disposición en capas en contacto con una composición de material hinchable para producir un núcleo sólido con dos o más capas, donde el núcleo está rodeado por una pared atóxica, membrana o recubrimiento, como por ejemplo una membrana semipermeable que permite el ingreso de un líquido acuoso en el núcleo y la salida de la sal de bupropion desde el núcleo hacia el exterior de la forma farmacéutica a través de al menos un pasadizo en la membrana semipermeable o por ósmosis y difusión a través de la membrana para permitir la comunicación del núcleo con el exterior de la forma farmacéutica para la administración de la sal de bupropion y se formula de manera tal que la forma farmacéutica presente una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y

después de 16 horas, se libera más de 80 % en peso de la sal de bupropion; o un dispositivo en el que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende un dispositivo de administración osmótica que comprende un núcleo y una membrana rodeando dicho núcleo, donde dicho núcleo contiene una cantidad terapéuticamente eficaz de la sal de bupropion, y opcionalmente al menos un medio para dispensar forzadamente la sal de bupropion desde el dispositivo, donde dicha membrana comprende al menos un medio para la salida de la sal de bupropion desde el dispositivo, donde dicho dispositivo se formula de manera tal que cuando el dispositivo está en un medio acuoso, la sal de bupropion, y opcionalmente al menos un medio para dispensar forzadamente la sal de bupropion desde el dispositivo y el al menos un medio para la salida de la sal de bupropion desde el dispositivo actúan cooperativamente para presentar una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion; o un dispositivo en el que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización, la forma farmacéutica de liberación modificada comprende un dispositivo de administración osmótica que comprende un núcleo y una membrana rodeando dicho núcleo, donde dicho núcleo contiene una cantidad terapéuticamente eficaz de la sal de bupropion, al menos un medio para aumentar la presión hidrostática dentro de la membrana y opcionalmente al menos un medio para dispensar forzadamente la sal de bupropion desde el dispositivo, donde dicha membrana comprende al menos un medio para la salida de la sal de bupropion desde el dispositivo, donde dicho dispositivo

se formula de manera tal que cuando el dispositivo está en un medio acuoso, el al menos un medio para aumentar la presión hidrostática dentro de la membrana y opcionalmente el al menos un medio para dispensar forzadamente la sal de bupropion desde el dispositivo actúan cooperativamente para presentar una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion; o un dispositivo en el que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos una realización la invención apunta a formulaciones de bromhidrato de bupropion de liberación sostenida para administrar una vez al día equivalentes según las pautas de la FDA a Wellbutrin™ ER o Zyban™/Wellbutrin™ SR cuando se administran una vez al día a un sujeto que los necesita y donde la sal de bupropion contenida es más estable que la sal clorhidrato de bupropion contenida en Welbutrin ER o Zyban, cuando se almacenan a 40 grados C y 75 % de humedad relativa durante al menos 3, 4, 5 y/o al menos 6 meses. Particularmente, la invención abarca formulaciones bioequivalentes que contienen 150 mg, 174 mg, 300 mg o 348 mg de bupropion HBr.

En al menos una realización la invención apunta a formulaciones tópicas que contienen bromhidrato de bupropion que se pueden administrar tópicamente p. ej. por vía transmucosa o transdérmica. Particularmente, la invención abarca geles y dispositivos de administración tipo parches tópicamente administrables que pueden comprender potencialmente otro principio activo como nicotina.

En al menos una realización la invención apunta a composiciones inhalables de administración pulmonar que contienen bromhidrato de bupropion que se pueden administrar por vía pulmonar a un sujeto que las

La invención, en al menos una realización, apunta a un método para administrar una sal de bupropion al aparato digestivo de un ser humano para el tratamiento o el manejo de una afección, donde el método comprende: (a) ingresar oralmente en el ser humano una forma farmacéutica de liberación modificada que comprende un núcleo y una membrana que rodea dicho núcleo, donde dicho núcleo comprende una sal de bupropion y opcionalmente un medio para dispensar forzadamente la sal de bupropion desde el dispositivo, donde dicha membrana comprende al menos un medio para la salida de la sal de bupropion desde la forma farmacéutica y (b) administrar la sal de bupropion desde la forma farmacéutica que se formula de forma tal que cuando la forma farmacéutica está en un medio acuoso, la sal de bupropion y opcionalmente el medio para dispensar forzadamente la sal de bupropion y el al menos un medio para la salida de la sal de bupropion actúan cooperativamente para presentar una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion; o un medicamento en el que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

La invención, en al menos una realización, apunta a un método para administrar una sal de bupropion al aparato digestivo de un ser humano para el tratamiento o el manejo de una afección, donde el método comprende: (a) ingresar oralmente en el ser humano una forma farmacéutica de liberación modificada que comprende un núcleo y una membrana que rodea dicho núcleo, donde dicho núcleo comprende la sal de bupropion, un medio para aumentar la presión hidrostática dentro del núcleo y opcionalmente un medio para dispensar forzadamente la sal de bupropion desde el dispositivo, donde dicha membrana comprende al menos un medio para la salida de la sal de bupropion desde la forma farmacéutica y (b) administrar la sal de bupropion desde la forma farmacéutica que se formula de forma tal que cuando la forma farmacéutica

necesita. Preferentemente, estas composiciones se producen de acuerdo con la tecnología del aerosol divulgada en las patentes de los Estados Unidos N° 6,682,716; 6,716,415; 6,716,417; 6,783,753; 7,029,658; y 7,033,575 y otras asignadas a Alexza Corporation. Estas patentes divulgan en particular el uso de dichos métodos para producir aerosoles que contienen antidepresivos para administración pulmonar.

En al menos una realización la invención apunta a composiciones inyectables que comprenden una cantidad eficaz de bromhidrato de bupropion y un vehículo o excipiente farmacéuticamente aceptable.

En al menos una realización, la invención apunta a un método para tratar una afección que comprende administrar cualquiera de las formas farmacéuticas osmóticas descritas antes a un paciente que necesita dicha administración una vez al día.

La invención, en al menos una realización, apunta a un método para administrar una sal de bupropion al tubo digestivo de un ser humano para el tratamiento o el manejo de una afección, donde el método comprende: (a) ingresar oralmente en el ser humano una forma farmacéutica de liberación modificada que contiene una sal de bupropion, donde la forma farmacéutica de liberación modificada comprende una forma farmacéutica osmótica; y (b) administrar la sal de bupropion desde la forma farmacéutica osmótica en una dosis que dé una respuesta terapéutica para producir el tratamiento o manejo de la afección de modo que la forma farmacéutica osmótica presente una velocidad de liberación in vitro tal que después de 2 horas, se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion, y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion, o una forma farmacéutica donde después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

está en un medio acuoso, la sal de bupropion, el medio para aumentar la presión hidrostática dentro del núcleo y opcionalmente el medio para dispensar forzadamente la sal de bupropion y el al menos un medio para la salida de la sal de bupropion actúan cooperativamente para presentar una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion; o un dispositivo en el que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos otra realización, la forma farmacéutica osmótica comprende además un recubrimiento de liberación inmediata para la liberación inmediata de la sal de bupropion desde el recubrimiento de liberación inmediata. En realizaciones que comprenden el recubrimiento de liberación inmediata, la forma farmacéutica osmótica presenta una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o una forma farmacéutica en la que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % o después de 16 horas se libera al menos 85 %.

En al menos otra realización, la forma farmacéutica 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 primer líquido externo, al mismo tiempo que es soluble en un segundo líquido externo. En realizaciones que comprenden el recubrimiento inerte soluble en agua, la forma farmacéutica osmótica presenta una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de

bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o una forma farmacéutica en la que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % o después de 16 horas se libera al menos 85 %.

En al menos otra realización, la forma farmacéutica osmótica comprende un subrecubrimiento osmótico. En realizaciones que comprenden el subrecubrimiento osmótico, la forma farmacéutica osmótica presenta una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o una forma farmacéutica en la que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos otra realización, las formas farmacéuticas osmóticas comprenden además un recubrimiento de control de la liberación. El recubrimiento de control de la liberación de la forma farmacéutica osmótica puede, por ejemplo, controlar, extender y/o retardar la liberación de la sal de bupropion. En realizaciones que comprenden el recubrimiento de control de la liberación, la forma farmacéutica osmótica presenta una velocidad de liberación in vitro tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después de 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion o una forma farmacéutica en la que después de 2 horas se libera no más de 40 %, después de 4 horas se libera de 40 % a 75 %, después de 8 horas se libera al menos 75 % y después de 16 horas se libera al menos 85 %.

En al menos otra realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende un material que es soluble en los jugos intestinales o erosionable por dichos jugos, fundamentalmente los líquidos de pH neutro o básico de los líquidos que tienen un pH superior al del líquido gástrico, pero en su mayor parte insolubles en los jugos gástricos o líquidos ácidos.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua y al menos un polímero soluble en agua.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua y al menos un polímero soluble en agua y opcionalmente al menos un plastificante.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua, al menos un polímero soluble en agua y al menos un medio para la salida de la sal de bupropion desde el núcleo de la forma farmacéutica osmótica.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua, al menos un polímero soluble en agua y al menos un pasadizo.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua, al menos un polímero soluble en agua y al menos un plastificante.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua, al menos un polímero soluble en agua, opcionalmente al menos un plastificante y al menos un medio para la salida de la sal de bupropion desde el núcleo de la forma farmacéutica osmótica.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende al menos un polímero formador de película, insoluble en agua y permeable al agua, al menos un polímero soluble en agua opcionalmente al menos un plastificante y al menos un pasadizo.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende una dispersión acuosa de un copolímero de un éster neutro sin ningún grupo funcional; un poliglicol con un punto de fusión mayor de 55°C, uno o más excipientes farmacéuticamente aceptables y opcionalmente al menos un medio para la salida de la sal de bupropion desde el núcleo de la forma farmacéutica osmótica. Este recubrimiento de control de la liberación se cura a una temperatura al menos mayor o igual que el punto de fusión del poliglicol.

En al menos otra realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica comprende un polímero entérico.

La membrana o pared es permeable al pasaje de medios acuosos pero no al pasaje de la sal de bupropion presente en el núcleo. La membrana puede ser por ejemplo, una membrana semipermeable o una membrana asimétrica, que puede ser permeable, semipermeable, perforada o no perforada y puede administrar la sal de bupropion mediante bombeo osmótico o los mecanismos combinados de difusión y bombeo osmótico. La integridad estructural de dichas membranas debe permanecer prácticamente intacta durante el período de administración de la sal de bupropion. Por "prácticamente intacta" se quiere dar a entender que la propiedad de semipermeable de la membrana

no está en riesgo durante el período de administración de la sal de bupropion.

La membrana semipermeable de la forma farmacéutica osmótica comprende al menos un excipiente farmacéuticamente aceptable, al menos un polímero, una cera o una combinación de éstos, aunque se pueden usar materiales inorgánicos tratados apropiadamente como cerámicas, metales o vidrios. Cuando la membrana semipermeable comprende al menos un polímero, el peso molecular del al menos un polímero o de la combinación de polímeros debe ser tal que el polímero o la combinación de polímeros sean sólidos a la temperatura de uso es decir, tanto in vitro como in vivo.

En ciertas realizaciones, el al menos un polímero incluido en la membrana semipermeable de la forma farmacéutica osmótica puede ser un éster de celulosa, como por ejemplo, acetato de celulosa, acetato acetoacetato de celulosa, acetato benzoato de 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 dimetilsulfamato 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 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 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, dipentanato de celulosa, dipentanlato de celulosa, formiato de celulosa, metacrilatos de celulosa, metoxibenzoato de celulosa, nitrato de celulosa, nitrobenzoato de celulosa, fosfato de 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 celulosa, trinitrato de celulosa, trioctanoato de celulosa, tripalmitato de celulosa, tripropionato de celulosa, trisuccinato de celulosa, trivalerato de celulosa, valerato palmitato de celulosa; un éter 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 dimetoxietilcelulosa, etil 2-hidroxiletil celulosa, etilcelulosa, sulfato de etilcelulosa, dimetilsulfamato de etilcelulosa, metilcelulosa, acetato de metilcelulosa, metil cianoetil celulosa, carboximetil 2-hidroxietilcelulosa sódica, carboximetilcelulosa sódica; una polisulfona, como por ejemplo, poliétersulfonas; un policarbonato; un poliuretano; un acetato de polivinilo; un alcohol polivinílico; un poliéster; un polialqueno como polietileno, copolímero de etileno y alcohol vinílico, polipropileno, poli(1,2-dimetil-1-butenileno), poli(1-bromo-1-butenileno), poli(1-buteno), poli(1-cloro-1-butenileno), 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, poli[(pentafluoroetil)etileno], poli[2-etilhexiloxi)etileno], poli(butiletileno), poli(tercbutiletileno), poli(cilclohexiletileno), poli[(ciclohexilmetil)etileno], 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-metilestireno), poli(isopentilestireno), poli(isopropilestireno), ésteres polivinílicos o éteres polivinílicos, como por ejemplo, poli(benzoiletileno), poli(butoxietileno), poli(cloropreno), poli(ciclohexiloxietileno), poli(deciloxietileno), poli(dicloroetileno), poli(difluoroetileno), poli(acetato de vinilo), poli(viniltrimetilestireno; un polisiloxano, como por ejemplo, poli(dimetilsiloxano); un derivado de ácido poliacrílico, como por ejemplo, poliacrilatos, polimetil metacrilato, poli ésteres de alquilos superiores de (ácido acrílico), 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 secbutilo), poli(acrilato de hexilo), poli(acrilato de octilo), 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 acrílicas; una poliamida, como por ejemplo, poli(iminoadipoiliminododecametileno), poli(iminoadipoiliminohexametileno), poliéteres, como por ejemplo, poli(octiloxietileno), 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 farmacéutica osmótica puede ser, por ejemplo, cera de

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 hoja de bambú, cera de candelilla, cera carnauba, cera de Japón, cera de ouricuri, cera de jojoba, cera del árbol de la cera, cera de abeto Douglas, cera de algodón, cera de arándano rojo, cera de cape berry, cera de cáscara de arroz, cera de ricino, cera de maíz indio, aceites vegetales hidrogenados (por ejemplo, de ricino, palma, semilla de algodón, soja), cera de grano de sorgo, cera de musgo español, cera de caña de azúcar, cera de caranda, cera blanqueada, cera de esparto, cera de lino, cera de Madagascar, cera de cáscara de naranja, cera de laca, cera de cáñamo y cera de arroz; ceras minerales, como por ejemplo, cera de Montan, ceras de turba, cera de petróleo, ceresina, ozocerita, cera microcristalina y parafinas; ceras sintéticas, como por ejemplo, cera de polietileno, cera de Fischer-Tropsch, ceras de hidrocarburos modificados químicamente, cera de ésteres de cetilo; y sus combinaciones.

En al menos una realización, la membrana semipermeable de la forma farmacéutica osmótica puede contener una combinación de al menos un polímero, cera o combinaciones de éstos y opcionalmente al menos un excipiente. El peso porcentual total de todos los componentes que forman la membrana semipermeable es 100 %.

En realizaciones en las que la sal de bupropion se libera a través de la membrana o pared de forma controlada mediante los mecanismos combinados de difusión y bombeo osmótico, la membrana o pared puede contener al menos uno de los polímeros y/o ceras antes descritos o una combinación de polímeros, como por ejemplo, ésteres de celulosa, copolímeros de sales de metacrilato y en forma opcional un plastificante.

Las sales de copolímero de poli(metacrilato) usadas en la fabricación de la membrana para la forma farmacéutica osmótica pueden ser, por ejemplo, insolubles en agua y en líquidos digestivos, pero son permeables en diferentes medidas. Algunos ejemplos de dichos copolímeros son copolímero RL de poli(metacrilato de amonio) (Eudragit® RL), copolímero de poli(metacrilato de amonio) (tipo A-

USP/NF), copolímero (RL-JSPI) de poli(metacrilato de aminoalquilo), y copolímero de (acrilato de etilo)-(metacrilato de metilo)-[etilmetacrilato de (trimetilamonio)] (1:2:0,2), PM 150.000. Otros ejemplos de dichos copolímeros incluyen los comercializados por Rohm Pharma, Weiterstadt, como, por ejemplo, Eudragit® RS 100: polímero sólido, Eudragit® RL 12.5: solución al 12,5 % en disolvente, Eudragit® RL 30 D: dispersión acuosa al 30 %, y otros productos equivalentes. También se pueden usar los siguientes copolímeros de poli(metacrilato de amonio): copolímero RS de metacrilato de amonio (Eudragit® RS), copolímero de poli(metacrilato de amonio) (tipo B-USP/NF), copolímero (RSL-JSP I) de poli(metacrilato de aminoalquilo), copolímero de (acrilato de etilo)-(metacrilato de metilo)-[etilmetacrilato de (trimetilamonio)] (1:2:0,1), PM 150.000. Entre los polímeros específicos se incluyen (Rohm Pharma, Weiterstadt):Eudragit® RS 100: polímero sólido, Eudragit® RS 12.5: solución al 12,5 % en disolvente, Eudragit® RD 30 D: dispersión acuosa al 30 %, y otros productos equivalentes. El RL es muy permeable al agua mientras que Eudragit® RS es apenas permeable al agua. Al emplear mezclas de Eudragit® RL y Eudragit® RS, se pueden preparar membranas que tengan el grado deseado de permeabilidad para lograr las velocidades de disolución in vitro y los parámetros farmacocinéticos in vivo.

El uso de plastificantes es opcional pero puede estar incluido en la forma farmacéutica osmótica para modificar las propiedades y las características de los polímeros usados en los recubrimientos o el núcleo de las formas farmacéuticas osmóticas para el procesamiento conveniente durante la fabricación de los recubrimientos y/o del núcleo de la forma farmacéutica osmótica, si fuera necesario. El término "plastificante" como se usa aquí incluye a todos los compuestos capaces de plastificar o ablandar un polímero o aglutinante usado en la invención. Una vez que se preparó el recubrimiento o membrana, ciertos plastificantes pueden actuar para aumentar la hidrofilicidad del o de los recubrimientos y/o del núcleo de la forma farmacéutica osmótica en el ambiente de uso. Durante la fabricación del recubrimiento, el plastificante puede ser capaz de reducir la temperatura

de fusión o la temperatura de la transición vítrea (temperatura del punto de ablandamiento) del polímero o aglutinante. Los plastificantes, como los PEG de bajo peso molecular, en general amplían el peso molecular promedio de un polímero en el cual están incluidos disminuyendo de ese modo su temperatura de transición vítrea o punto de ablandamiento. Los plastificantes también pueden reducir la viscosidad de un polímero. El plastificante puede impartir algunas propiedades físicas particularmente ventajosas al dispositivo osmótico de la invención.

Los plastificantes útiles en la forma farmacéutica osmótica de la invención incluyen, por ejemplo, polímeros de bajo peso molecular, oligómeros, copolímeros, aceites, moléculas orgánicas pequeñas, polioles de bajo peso molecular con hidroxilos alifáticos, plastificantes tipo éster, ésteres de glicol, poli(propilenglicol), polímeros multibloque, polímeros de bloque único, polietilenglicoles de bajo peso molecular, plastificantes tipo éster de citrato, triacetina, propilenglicol, glicerina, etilenglicol, 1,2-butilenglicol, 2,3-butilenglicol, estirenglicol, dietilenglicol, trietilenglicol, tetraetilenglicol y otros compuestos de poli(etilenglicol), éter monoisopropílico de monopropilenglicol, éter monoetílico de propilenglicol, éter monoetílico de etilenglicol, éter monoetílico de dietilenglicol, lactato de sorbitol, lactato de etilo, lactato de butilo, glicolato de etilo, sebacato de dibutilo, acetil tributil citrato, citrato de trietilo, acetil trietil citrato, citrato de tributilo y glicolato de alilo. Todos estos plastificantes se encuentran disponibles en el mercado de proveedores como Aldrich o Sigma Chemical Co. También se contempla y se considera dentro del alcance de la invención, la posibilidad de usar una combinación de plastificantes en la presente formulación. Los plastificantes a base de PEG están disponibles en el mercado o se pueden preparar por diversos métodos, como se describe en Poly(ethylene glycol) Chemistry: Biotechnical and Biomedical Applications (J.M. Harris, Ed.; Plenum Press, NY). Una vez que se fabrica la forma farmacéutica osmótica, ciertos plastificantes pueden actuar para aumentar la hidrofilicidad de los recubrimientos y/o del núcleo de la

forma farmacéutica osmótica en el ambiente de uso, sea in vitro o in vivo. Consecuentemente, algunos plastificantes pueden actuar como mejoradores del flujo.

La relación ésteres de celulosa:copolímeros de sales de metacrilato:plastificante de las formas farmacéuticas osmóticas puede ser, por ejemplo, de 1-99 % en peso de éster de celulosa:84-0,5 % en peso de los copolímeros de sal de metacrilato:15-0,5 % en peso del plastificante. El peso porcentual total de todos los componentes que forman la pared es de 100 %.

Aparte de las membranas semipermeables de la forma farmacéutica osmótica descrita antes, también se pueden usar membranas asimétricas para rodear el núcleo de una forma farmacéutica osmótica para la liberación controlada de la sal de bupropion para proporcionar las velocidades de liberación in vitro descritas antes y los parámetros farmacocinéticos terapéuticamente beneficiosos in vivo para el tratamiento o el manejo de una afección. Dichas membranas asimétricas pueden ser permeables, semipermeables, perforadas o no perforadas y pueden liberar la sal de bupropion mediante bombeo osmótico, difusión o los mecanismos combinados de difusión y bombeo osmótico. El lector puede consultar la patente de los Estados Unidos N° 5,612,059 acerca de la fabricación y el uso de las membranas asimétricas para la liberación controlada de un ingrediente activo a través de una o más membranas asimétricas por ósmosis o por una combinación de difusión y bombeo osmótico.

En algunas realizaciones de la forma farmacéutica osmótica, la membrana semipermeable puede contener además un mejorador del flujo o agente generador de canales.

Los "agentes mejoradores del flujo" o "agentes generadores de canales" son materiales que actúan aumentando el volumen de líquido embebido en el núcleo para permitir que la forma farmacéutica osmótica dispense prácticamente toda la sal de bupropion a través de al menos un pasadizo en la membrana semipermeable, por ósmosis o por ósmosis y difusión a través de la membrana semipermeable. El agente mejorador del flujo se disuelve para formar caminos en la membrana semipermeable para que

el líquido ingrese en el núcleo y disuelva la sal de bupropion en el núcleo junto con el osmoagente, si hay uno presente, pero no permita la salida de la sal de bupropion. El agente mejorador del flujo puede ser cualquier material soluble en agua o un material entérico que permita un aumento en el volumen de líquido embebido en el núcleo 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 ftalato de celulosa, alcoholes polivinílicos, copolímeros metacrílicos y sus combinaciones. Algunos plastificantes pueden actuar como mejoradores del flujo aumentando la hidrofilicidad de la membrana semipermeable y/o el núcleo de la forma farmacéutica osmótica. Los mejoradores del flujo o agentes formadores de canales también pueden actuar como un medio para la salida de la sal de bupropion desde el núcleo si el agente mejorador del flujo o formador de canales se usa en una cantidad suficiente.

La expresión "pasadizo" como se usa aquí comprende medios y métodos adecuados para la liberación medida de la sal de bupropion desde el núcleo de la forma farmacéutica osmótica. Los medios para la salida de la sal 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 de bupropion. El medio para la salida puede ser lineal o tortuoso. Los medios para la salida incluyen un área debilitada de la membrana semipermeable o un material que sea erosionado o lixiviado de la pared en un ambiente líquido de uso para producir al menos un pasadizo unidimensional. El medio para la salida de la sal de bupropion puede incluir cualquier material lixiviable, que cuando se lixivia de la membrana semipermeable forma un pasadizo adecuado para la salida de la sal de bupropion desde el núcleo de la forma farmacéutica osmótica. Dichos materiales lixiviables pueden contener, por ejemplo, un ácido poli(glicólico) lixiviable o un polímero del ácido

poli(láctico) en la membrana semipermeable, un filamento gelatinoso, poli(vinil alcohol), polisacáridos lixiviables, sales, óxidos, sorbitol sacarosa. El medio para la salida también puede contener un mejorador del flujo o agente formador de canales si está presente en cantidad suficiente. El medio para la salida posee dimensiones de liberación controlada, como redonda, triangular, cuadrada y elíptica, para la liberación regulada de la sal de bupropion desde la forma farmacéutica. Las dimensiones del medio para la salida de la sal de bupropion tienen el tamaño adecuado para permitir que la sal de bupropion pase a través del medio para la salida. La forma farmacéutica se puede elaborar con uno o más medios para la salida en una relación de separación espacial en una superficie única o en más de una superficie de la pared.

La expresión "ambiente líquido" denota un líquido acuoso o biológico como en un paciente humano, incluido el tubo digestivo. El medio para la salida puede ser preformado, por ejemplo, por medios mecánicos después de que la membrana semipermeable se aplica al núcleo de la forma farmacéutica osmótica, tal como por ejemplo, mediante perforación mecánica, perforación con láser, o usando una saliente del tamaño adecuado en el interior del punzón de comprimidos para formar el medio para la salida de la sal de bupropion, como por ejemplo, una punta cilíndrica o cónica trunca que forme parte integral de la superficie interior del punzón superior de un punzón usado para formar la forma farmacéutica osmótica. Como alternativa, el medio para la salida de la sal de bupropion se puede formar incorporando un material lixiviable o un formador de poros en la composición semipermeable antes de aplicar la membrana semipermeable al núcleo de la forma farmacéutica osmótica. El medio para la salida de la sal de bupropion puede comprender una combinación de los diferentes medios para la salida descritos antes. La forma farmacéutica osmótica puede contener más de un medio para la salida de la sal de bupropion incluidos dos, tres, cuatro, cinco, seis, siete, ocho, nueve, diez o más medios para la salida y se pueden formar en cualquier lugar de la forma farmacéutica osmótica. Las diferentes posiciones de los medios para la salida se describen, por ejemplo en la patente de los Estados

Unidos N° 6,491,949. El tipo, la cantidad y las dimensiones de los medios para la salida de la sal de bupropion son tales que la forma farmacéutica presenta las velocidades de liberación deseadas in vitro descritas aquí y pueden ser determinados por los técnicos con experiencia en liberación de fármacos mediante los experimentos de rutina. Los medios para la salida y el equipo para formar dichos medios para la salida se describen por ejemplo, en las patentes de los Estados Unidos N° 3,845,770; 3,916,899; 4,034,758; 4,063,064; 4,077,407; 4,088,864; 4,200,098; 4,285,987; 4,783,337; 4,816,263 y 5,071,607.

El dispositivo osmótico también puede contener un recubrimiento de control de la liberación rodeando la membrana semipermeable que comprende un recubrimiento entérico o de liberación retardada que es soluble o erosionable en los jugos intestinales, fundamentalmente en los líquidos de pH neutro o básico de los líquidos que tienen un pH mayor que el del jugo gástrico, pero en su mayor parte insoluble en jugos gástricos o líquidos ácidos. Se conoce una amplia variedad de otros materiales poliméricos que poseen estas diversas propiedades de solubilidad. Entre esos otros materiales poliméricos se incluyen, por ejemplo, acetato ftalato de celulosa (CAP), acetato trimeletato de celulosa (CAT), ftalato de poli(acetato de vinilo) (PVAP), ftalato de hidroxipropilmetilcelulosa (HP), copolímero de poli(metacrilato acrilato de etilo) (1:1) (MA-EA), copolímero de poli(metacrilato metacrilato de metilo) (1:1) (MA-MMA), copolímero de poli(metacrilato metacrilato de metilo) (1:2), Eudragit® L-30-D (MA-EA, 1:1), Eudragit® L-100-55 (MA-EA, 1:1), acetato succinato de hidroxipropilmetilcelulosa (HPMCAS), Coateric® (PVAP), Aquateric® (CAP), AQUACOAT® (HPMCAS) y sus combinaciones. El recubrimiento entérico también puede contener auxiliares de disolución, modificadores de la estabilidad y potenciadores de la bioabsorción.

Cuando se desee que el recubrimiento de control de la liberación de las formas farmacéuticas osmóticas de la presente invención se disuelvan, erosionen o desprendan de la forma farmacéutica osmótica, se pueden usar materiales como hidroxipropilcelulosa, celulosa

microcristalina (MCC, Avicel™ de FMC Corp.), copolímero de poli (etilen-acetato de vinilo) (60:40) (EVAC de Aldrich Chemical Co.), 2-hidroxietilmetacrilato (HEMA), MMA, terpolímeros de HEMA:MMA:MA sintetizados en presencia de N,N'-bis (metacriloiloxietiloxicarbonilamino)-azobenceno, azopolímeros, sistema de liberación temporizada con recubrimiento entérico (Time Clock® de Pharmaceutical Profiles, Ltd., Reino Unido) y pectinato de calcio.

Los polímeros para usar en el recubrimiento de control de la liberación de las formas farmacéuticas osmóticas de la presente invención pueden ser, por ejemplo, materiales entéricos que resisten la acción del líquido gástrico evitando la penetración a través de la pared semipermeable mientras uno o más de los materiales del núcleo de la forma farmacéutica se solubilizan en el intestino y permitiendo así que comience la liberación de la sal de bupropion del núcleo mediante bombeo osmótico de la forma farmacéutica osmótica. Un material que se adapta a este tipo de requisitos puede ser, por ejemplo, un copolímero de poli(vinilpirrolidona)-acetato de vinilo, como el material comercializado por BASF con la marca Kollidon® VA64, mezclado con estearato de magnesio y otros excipientes similares. El recubrimiento entérico también puede contener povidona, comercializada por BASF con la marca Kollidon® K 30, e hidroxipropilmetilcelulosa, comercializada por Dow con la marca Methocel® E-15. Los materiales se pueden preparar en soluciones que tengan diferentes concentraciones de polímero de acuerdo con la viscosidad deseada de la solución. Por ejemplo, una solución acuosa al 10 % P/V de Kollidon® K 30 tiene una viscosidad de 5,5-8,5 cp a 20°C y una solución acuosa al 2 % P/V de Methocel® E-15 tiene una viscosidad de 13-18 cp a 20°C.

El recubrimiento de control de la liberación de las formas farmacéuticas osmóticas de la presente invención pueden comprender uno o más materiales que no se disuelven, desintegran ni cambian su estructura integral en el estómago durante el período durante el cual el comprimido reside en el estómago, como un ejemplo elegido entre el grupo de (a) queratina, queratina sandarac-tolú, salol (salicilato de fenilo), beta naftilbenzoato de

salol y acetotanino, salol con bálsamo de Perú, salol con tolú, salol con goma mástica, salol y ácido estéarico, y salol y goma laca; (b) un miembro elegido entre el grupo de proteína formalizada, gelatina formalizada y gelatina formalizada reticulada y resinas de intercambio; (c) un miembro elegido entre el grupo de ácido mirístico-aceite de ricino hidrogenado-colesterol, ácido esteárico-sebo de oveja, ácido esteárico-bálsamo de tolú, y ácido esteárico-aceite de ricino; (d) un miembro elegido entre el grupo de goma laca, goma laca amoniacal, goma laca amoniacal-salol, goma laca-grasa de lana, goma laca-acetilalcohol, goma laca-ácido esteárico-bálsamo de tolú, y goma laca estearato de n-butilo; (e) un miembor elegido entre el grupo de ácido abiético, abietato de metilo, benzoína, bálsamo de tolú, sandarac, goma mástica con tolú, y goma mástica con tolú, y goma mástica con acetilalcohol; (f) resinas acrílicas representadas por polímeros aniónicos sintetizados a partir del ácido metacrílico y éster metílico del ácido metacrílico, resinas acrílicas copoliméricas del ácido metacrílico y ácido metacrílico y ésteres alquílicos del ácido metacrílico, copolímeros de ácido alcacrílico y ésteres alquílicos del ácido alcacrílico, resinas acrílicas tales como copolímero de aminoetilmetacrilato de dimetilo-metacrilato de butilo-metacrilato de metilo de peso molecular 150.000, copolímero de ácido metacrílico-metacrilato de metilo 50:50 de peso molecular 135.000, copolímero de ácido metacrílico-metacrilato de metilo 30:70 de P.M. 135.000, ácido metacrílico-aminoetilmetacrilato de dimetilo-acrilato de etilo de P.M. 750.000, ácido metacrílico-metacrilato de metilo-acrilato de etilo de P.M. 1.000.000, y acrilato de etilo-metacrilato de metilo-acrilato de etilo de P.M. 550.000; y, (g) una composición elegida entre el grupo de acetilftalato de celulosa, diacetilftalato de celulosa, triacetilftalato de celulosa, acetato ftalato de celulosa, ftalato de hidroxipropil metilcelulosa, acetato ftalato de celulosa sódica, ftalato de éster de celulosa, ftalato de éter de celulosa, ftalato de metilcelulosa, ftalato de éster-éter de celulosa, ftalato de hidroxipropil celulosa, sales alcalinas de acetato ftalato de celulosa, sales alcalinotérreas de acetato ftalato de celulosa, sal de calcio de acetato ftalato de celulosa, sal de amonio de ftalato de

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hidroxipropilmetilcelulosa, acetato hexahidroftalato de celulosa, hexahidroftalato de hidroxipropilmetilcelulosa, acetato ftalato de polivinilo, ftalato de dietilo, ftalato de dibutilo, ftalato de dialquilo en el cual el alquilo comprende de 1 a 7 grupos alquilo lineales y ramificados, ftalatos de arilo y otros materiales conocidos por los técnicos con experiencia en el área.

Por consiguiente, en al menos otra realización, el recubrimiento de control de la liberación de las formas farmacéuticas osmóticas de la presente invención contiene un polímero formador de película insoluble en agua y permeable al agua, un polímero soluble en agua y opcionalmente un plastificante y/o un formador de poros. Los polímeros formadores de película insolubles en agua y permeables al agua útiles para la fabricación del recubrimiento de control de la liberación pueden ser éteres de celulosa, como por ejemplo, etilcelulosas elegidas entre el grupo de etilcelulosa grado PR 100, etilcelulosa grado PR 20 y cualquiera de sus combinaciones, ésteres de celulosa y alcohol polivinílico. Los polímeros solubles en agua útiles para el recubrimiento de control de la liberación pueden ser, por ejemplo, polivinilpirrolidona, hidroxipropilmetilcelulosa e hidroxipropilcelulosa.

El técnico con experiencia apreciará que las velocidades de liberación in vitro deseadas descritas aquí para la sal de bupropion se pueden lograr controlando la permeabilidad y/o la cantidad del recubrimiento aplicado al núcleo de la forma farmacéutica osmótica. La permeabilidad del recubrimiento de control de la liberación se puede alterar variando la relación entre polímero formador de película insoluble en agua y permeable al agua:polímero soluble en agua:plastificante opcional y/o la cantidad de recubrimiento aplicada al núcleo de la forma farmacéutica osmótica. Una liberación más extendida se obtiene generalmente con una mayor cantidad de polímero formador de película insoluble en agua y permeable al agua. La adición de otros excipientes al núcleo de la forma farmacéutica osmótica también puede alterar la permeabilidad del recubrimiento de control de la liberación. Por ejemplo, si el núcleo de la forma farmacéutica contiene un polímero hinchable, la cantidad

de plastificante del recubrimiento de liberación controlada se puede aumentar para hacer que el recubrimiento sea más flexible dado que la presión ejercida en un recubrimiento menos flexible por parte del polímero hinchable podría romper el recubrimiento. Además, la proporción del polímero insoluble en agua y permeable al agua y el polímero soluble en agua también se puede alterar dependiendo de si se desea una disolución in-vitro más rápida o más lenta.

En al menos otra realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica contiene una dispersión acuosa de un copolímero de un éster neutro sin ningún grupo funcional; un poliglicol con un punto de fusión mayor de 55° C, y uno o más excipientes farmacéuticamente aceptables y se cura a una temperatura al menos mayor o igual que el punto de fusión del poliglicol. La fabricación y el uso de dichas formulaciones de recubrimiento se describen en detalle en la solicitud publicada de la patente de los Estados Unidos 20040037883A1, publicada el 26 de febrero de 2004. En resumen, los ejemplos de copolímeros de ésteres neutros sin grupos funcionales comprendidos en el recubrimiento pueden ser Eudragit® NE30D, Eudragit® NE40D (Röhm America LLC), o sus mezclas. Este recubrimiento puede contener agentes hidrófilos para promover la humectación del recubrimiento cuando está en contacto con los fluidos gastrointestinales. Dichos agentes hidrofílicos incluyen, por ejemplo, polímeros hidrófilos 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, éteres alquílicos de polioxietileno, y estearatos de polioxietileno, y sus combinaciones. Este recubrimiento de control de la liberación de la forma farmacéutica osmótica puede contener además un formador de poros. Sin embargo, el formador de poros debe ser suficientemente insoluble en la dispersión acuosa, pero debe ser suficientemente soluble en el ambiente de uso. Un método para producir dichos recubrimientos se detalla en la patente europea EP 1267842B1.

El recubrimiento de control de la liberación de ciertas realizaciones de la forma farmacéutica osmótica de ciertas realizaciones de la presente invención incluye al menos un polímero en una cantidad suficiente para lograr una liberación controlada de la sal de bupropion. Otros ejemplos de polímeros que se pueden usar en el recubrimiento de control de la liberación de estas realizaciones incluyen acetato ftalato de celulosa, acetato trimaleato de celulosa, ftalato de hidroxipropilmetilcelulosa, acetato ftalato de polivinilo, copolímeros de metacrilato de amonio como los comercializados bajo la marca registrada Eudragit® RS y RL, copolímeros de ácido poliacrílico y poliacrilato y metacrilato como los comercializados bajo la marca registrada Eudragit® S y L, acetato de polivinil acetaldietilamino, acetato succinato de hidroxipropilmetilcelulosa, goma laca; hidrogeles y materiales que forman geles, como polímeros carboxivinílicos, alginato de sodio, carmelosa de sodio, carmelosa de calcio, carboximetil almidón sódico, alcohol polivinílico, hidroxietilcelulosa, metilcelulosa, gelatina, almidón y polímeros reticulados a base de celulosa en los que el grado de reticulación es bajo de modo de facilitar la adsorción de agua y la expansión de la matriz polimérica, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, almidón reticulado, celulosa microcristalina, quitina, copolímero aminoacril-metacrilato (Eudragit® RS-PM, Rohm & Haas), pullulan, colágeno, caseína, agar, goma arábiga, carboximetilcelulosa de sodio, (polímeros 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 aniónicos y catiónicos, alcohol polivinílico con bajo contenido de acetato residual, una mezcla hinchable de agar y carboximetilcelulosa, copolímeros de anhídrido maleico y estireno, etileno, propileno o isobutileno, pectina (peso molecular 30 k a 300 k), polisacáridos como agar, goma de acacia, goma karaya, goma tragacanto, alginas y goma guar, poliacrilamidas, óxidos de polietileno Polyox® (peso molecular de 100 k a 5.000 k), polímeros de acrilato AquaKeep®, diésteres de poliglucano, alcohol polivinílico y poli N-vinil-2-pirrolidona reticulados,

glicolato de almidón sódico (p. ej. Explotab®; Edward Mandell C. Ltd.); polímeros hidrófilos como los polisacáridos, metilcelulosa, carboximetilcelulosa de sodio o de calcio, hidroxipropilmetilcelulosa, hidroxipropilcelulosa, hidroxietilcelulosa, nitrocelulosa, carboximetilcelulosa, éteres de celulosa, óxidos de polietileno (p. ej. Polyox®, Union Carbide), metil etil celulosa, etil hidroxietil celulosa, acetato de celulosa, butirato de celulosa, propionato de celulosa, gelatina, colágeno, almidón, maltodextrina, pullulan, polivinilpirrolidona, alcohol polivinílico, acetato de polivinilo, ésteres de ácidos grasos de glicerol, poliacrilamida, ácido poliacrílico, copolímeros de ácido metacrílico o ácido metacrílico (p. ej. Eudragit®, Rohm y Haas), otros derivados del ácido acrílico, ésteres de sorbitán, gomas naturales, lecitinas, pectina, alginatos, alginato de amonio, alginatos de sodio, calcio y potasio, alginato de propilenglicol, agar y gomas como arábiga, karaya, de algarrobo, tragacanto, carrageninas, guar, xantano, escleroglucano y sus mezclas y combinaciones. En al menos una realización de la forma farmacéutica osmótica de la presente invención, el polímero es una dispersión de acrilato como Eudragit® NE30D, Eudragit® NE40D (Rohm America LLG), Kollicoat® SR 30D, Surelease® o una mezcla de éstos. El polímero puede estar presente en una cantidad entre 20 % y 90 % en peso del recubrimiento de control de la liberación, dependiendo del perfil de liberación controlada deseado. Por ejemplo, en ciertas realizaciones de la forma farmacéutica osmótica, el polímero está presente en una cantidad entre 50 % y 95 %, en otras realizaciones entre 60 % y 90 % y aún en otras realizaciones en 75 % del peso del recubrimiento de control de la liberación.

El recubrimiento de control de la liberación de ciertas realizaciones de la forma farmacéutica osmótica de la presente invención también puede incluir uno o más excipientes farmacéuticamente aceptables como lubricantes, emulsionantes, antiespumantes, plastificantes, disolventes y similares.

Se pueden incluir lubricantes en el recubrimiento de control de la liberación de ciertas realizaciones de la

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realizaciones el emulsionante está presente en una cantidad entre 0,01 % y 0,15 %, en otras realizaciones entre 0,01 % y 0,07 % y aún en otras realizaciones en 0,03 % del peso del recubrimiento de control de la liberación.

Se pueden incluir uno o más antiespumantes en el recubrimiento de control de la liberación de la forma farmacéutica osmótica de ciertas realizaciones de la presente invención para reducir la formación de burbujas o de espuma durante la fabricación del recubrimiento. Los antiespumantes útiles para la composición del recubrimiento de control de la liberación de la forma farmacéutica osmótica incluyen, pero no exclusivamente, simeticona, poliglicol y aceite de silicio. En al menos una realización el antiespumante es Simeticona C. El antiespumante puede estar presente en una cantidad entre 0,01 % y 10 % del peso del recubrimiento de control de la liberación. Por ejemplo, en ciertas realizaciones el antiespumante está presente en una cantidad entre 0,05 % y 1 %, en otras realizaciones entre 0,1 % y 0,3 % y aún en otras realizaciones en 0,15 % del peso del recubrimiento de control de la liberación.

Se contempla que en ciertas realizaciones, se pueden usar otros excipientes compatibles con los objetivos de la presente invención en el recubrimiento de control de la liberación de la forma farmacéutica osmótica.

En al menos una realización, el recubrimiento de control de la liberación de la forma farmacéutica osmótica incluye 75 % de Eudragit® NE30D, 1,5 % de estearato de magnesio, 1,5 % de talco, 0,03 % de Tween™ 80, 0,15 % de Simeticona C y 21,82 % de agua, en peso de la composición del recubrimiento de control de la liberación.

En un ejemplo profético de ciertas realizaciones de la forma farmacéutica osmótica de la presente invención, el proceso de fabricación del recubrimiento de control de la liberación de la forma farmacéutica osmótica puede ser hipotéticamente el siguiente: Se divide agua en dos porciones de 15 % y 85 %. Después se agregan el antiespumante y el emulsionante a la porción de 15 % de agua y se mezclan a 300 rpm para formar la porción A. En

forma farmacéutica osmótica de la presente invención para ayudar a reducir la fricción de las micropartículas recubiertas durante la fabricación. Los lubricantes que se pueden usar en el recubrimiento de control de la liberación incluyen, pero no exclusivamente, ácido adípico, 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 fumarato de sodio, aceite mineral liviano, ésteres de ácidos grasos como behenato de glicerilo, (es decir Compritol™), Stear-O-Wet™ y Myvatex™ TL. En al menos una realización, el lubricante se selecciona entre estearato de magnesio y talco. Las combinaciones de estos lubricantes son factibles. El o los lubricantes pueden estar presentes cada uno en una cantidad entre 0,1 % y 80 % del peso del recubrimiento de control de la liberación. Por ejemplo, en ciertas realizaciones el lubricante está presente en una cantidad entre 0,5 % y 20 %, en otras realizaciones entre 0,8 % y 10 % y aún en otras realizaciones en 1,5 % del peso del recubrimiento de control de la liberación.

Se pueden incluir uno o más emulsionantes (también denominados emulsificantes o emulgentes) en el recubrimiento de control de la liberación de las formas farmacéuticas osmóticas de ciertas realizaciones de la presente invención para facilitar la emulsificación real durante la fabricación del recubrimiento y también para aumentar o asegurar la estabilidad de la emulsión durante la vida útil del producto. Los emulsionantes útiles para la composición del recubrimiento de control de la liberación de la forma farmacéutica osmótica incluyen, pero no exclusivamente, materiales de origen natural y sus derivados semisintéticos, como los polisacáridos, así como ésteres de glicerol, éteres de celulosa, ésteres de sorbitán (por ejemplo, monooleato de sorbitán o Span™ 80) y polisorbatos (por ejemplo, Tween™ 80). Las combinaciones de emulsionantes son factibles. El o los emulsionantes pueden estar presentes en una cantidad entre 0,01 % y 0,25 % del peso del recubrimiento de control de la liberación. Por ejemplo, en ciertas

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al menos una realización, el antiespumante es Simeticona C y el emulsionante es Tween™ 80. Después se agrega un primer lubricante a la porción 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. Después 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 realización, el segundo lubricante es estearato de magnesio. Finalmente, se agrega una dispersión acuosa de un copolímero de un éster neutro y se mezcla durante 30 minutos a 500 rpm. En al menos una realización, la dispersión acuosa de un copolímero de un éster neutro es Eudragit® NE30D. La solución de recubrimiento resultante se puede usar entonces para recubrir las micropartículas osmóticas subrecubiertas hasta un aumento de peso del 35 % con los parámetros siguientes: Una temperatura de entrada entre 10°C y 60°C, preferentemente entre 20°C y 40°C, y más preferentemente entre 25°C y 35°C; una temperatura de salida entre 10°C y 60°C, preferentemente entre 20°C y 40°C, y más preferentemente entre 25°C y 35°C; una temperatura del producto entre 10°C y 60°C, preferentemente entre 15°C y 35°C, y más preferentemente entre 22°C y 27°C; un flujo de aire entre 10 m^3/h y 180 m^3/h, preferentemente entre 40 m^3/h y 120 m^3/h y más preferentemente entre 60 m^3/h y 80 m^3/h; y una presión de pulverización entre 0,5 bar y 4,5 bar, preferentemente entre 1 bar y 3 bar y más preferentemente de 2 bar. Las micropartículas recubiertas resultantes se pueden descargar entonces desde la cámara de recubrimiento y curar en estufa con los parámetros siguientes: Una temperatura de curado entre 20°C y 65°C, preferentemente entre 30°C y 55°C y más preferentemente de 40°C; y un tiempo de curado entre 2 horas y 120 horas, preferentemente entre 10 horas y 40 horas y más preferentemente de 24 horas. También se puede usar cualquier otra tecnología que dé como resultado la formulación de recubrimiento del recubrimiento de control de la liberación de la forma farmacéutica osmótica que es compatible con los objetivos de la invención.

En al menos otra realización, las formas farmacéuticas osmóticas comprenden un recubrimiento soluble en agua o recubrimiento de rápida disolución entre la membrana

semipermeable y el recubrimiento de control de la liberación. El recubrimiento de rápida disolución puede ser soluble en la cavidad bucal y/o en el tubo digestivo alto como estómago, duodeno, yeyuno o intestino delgado alto. Los materiales adecuados para la fabricación del recubrimiento soluble en agua se divulgan en las patentes de los Estados Unidos N°. 4,576,604 y 4,673,405 y el libro Pharmaceutical Dosage Forms: Tablets Volumen I, Segunda Edición. A. Lieberman. ed. 1989, Marcel Dekker, Inc. En ciertas realizaciones, el recubrimiento de rápida disolución puede ser soluble en saliva, jugos gástricos o líquidos ácidos. Los materiales que son adecuados para preparar el recubrimiento o capa soluble en agua pueden comprender, por ejemplo, gomas polisacáridas solubles en agua como carragenina, fucoidan, goma ghatti, goma tragacanto, arabinogalactano, pectina y goma xantano; sales de gomas polisacáridas 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 1 a 7 carbonos como, por ejemplo, hidroximetilcelulosa, hidroxietilcelulosa, e hidroxipropilcelulosa; formadores de láminas sintéticos a base de celulosa, solubles en agua, como, por ejemplo, metilcelulosa y sus derivados hidroxialquilmetilcelulosa como los miembros elegidos entre el grupo de hidroxietilmetilcelulosa, hidroxipropilmetilcelulosa e hidroxibutilmetilcelulosa; croscarmelosa de sodio otros polímeros de celulosa como carboximetilcelulosa sódica; y otros materiales conocidos por los técnicos con experiencia en el área. Otros materiales formadores de láminas que se pueden usar con este propósito incluyen, por ejemplo, poli(vinilpirrolidona), alcohol polivinílico, óxido de polietileno, una mezcla de gelatina y polivinilpirrolidona, gelatina, glucosa, sacáridos, povidona, copovidona, copolímero de poli(vinilpirrolidona)-poli(acetato de vinilo). El recubrimiento soluble en agua puede comprender otros excipientes farmacéuticos que alteran o no alteran la forma en que se comporta el recubrimiento soluble en agua. El técnico con experiencia reconocerá que los materiales indicados antes incluyen polímeros formadores de película. El recubrimiento inerte soluble en agua que cubre la pared semipermeable y bloquea el pasadizo de las

formas farmacéuticas osmóticas de la presente invención, se hace de material natural o sintético, el cual mediante disolución o erosión selectiva puede permitir el desbloqueo del pasadizo permitiendo de ese modo que comience el proceso de administración osmótica. Este recubrimiento soluble en agua puede ser impermeable a un primer líquido externo, al mismo tiempo que es soluble en un segundo líquido externo. Esta propiedad puede ayudar a alcanzar una liberación controlada y selectiva de la sal de bupropion desde la forma farmacéutica osmótica de modo de alcanzar las velocidades de liberación in vitro deseadas.

En realizaciones en las que el núcleo de la forma farmacéutica osmótica no comprende un osmoagente, las formas farmacéuticas osmóticas pueden comprender un subrecubrimiento osmótico, que puede rodear el núcleo de la forma farmacéutica osmótica. El subrecubrimiento osmótico comprende al menos un agente osmótico y al menos un polímero hidrófilo. El subrecubrimiento osmótico de esta realización asegura la separación sustancial de la sal de bupropion del agente osmótico en compartimientos/capas sustancialmente separados. Esta separación puede aumentar la estabilidad de la sal de bupropion reduciendo las posibles interacciones desfavorables entre la sal de bupropion y el osmoagente y/o entre la sal de bupropion y los componentes del recubrimiento de control de la liberación. Por ejemplo, el osmoagente puede ser de naturaleza higroscópica y puede atraer agua que puede dar lugar a la degradación de la sal de bupropion. Puesto que el agente osmótico de estas realizaciones se puede separar sustancialmente de la sal de bupropion, la sal de bupropion puede ser menos propensa a la degradación por el agua atraída por el osmoagente. El recubrimiento de control de la liberación comprende un polímero con control de la liberación y opcionalmente un plastificante. Los núcleos recubiertos de la forma farmacéutica osmótica se puede usar para llenar cápsulas, o alternativamente se pueden comprimir en forma de comprimidos usando excipientes adecuados. En estas realizaciones la forma farmacéutica osmótica multiparticulada puede utilizar tanto la difusión como la ósmosis para controlar la liberación del fármaco y se puede incorporar en las formas farmacéuticas de

liberación sostenida y/o de liberación retardada. Además, en ciertas realizaciones el gradiente de presión osmótica y la velocidad de liberación de la sal de bupropion se pueden controlar variando el nivel del agente osmótico y/o el nivel del polímero hidrófilo en el subrecubrimiento osmótico, sin la necesidad de un recubrimiento sellador alrededor del subrecubrimiento osmótico.

El polímero hidrófilo usado en un subrecubrimiento osmótico de ciertas realizaciones de la presente invención funciona como un vehículo para el agente osmótico. En ciertas realizaciones el polímero hidrófilo en el subrecubrimiento osmótico no afecta de manera importante a la liberación del fármaco. En al menos una realización, el polímero hidrófilo usado en el subrecubrimiento osmótico no actúa como una barrera contra la difusión para la liberación de la sal de bupropion. En al menos una realización el perfil de liberación del agente osmótico es prácticamente el mismo que el perfil de liberación de la sal de bupropion. Dichos polímeros hidrófilos útiles en un subrecubrimento osmótico de la presente invención incluyen a modo de ejemplo, polivinilpirrolidona, hidroxietilcelulosa, hidroxipropilcelulosa, hidroxipropilmetilcelulosa (HPMC) de bajo peso molecular, polimetacrilato, etilcelulosa y sus mezclas. En al menos una realización, el polímero hidrófilo del subrecubrimiento osmótico es un polímero hidrófilo de bajo peso molecular y baja viscosidad. Se puede usar una amplia gama de polímeros hidrófilos de bajo peso molecular y baja viscosidad en el subrecubrimiento osmótico. Los ejemplos de polímeros de HPMC que se pueden usar en el subrecubrimiento osmótico incluyen Pharmacoat® 606, Pharmacoat® 606G, Pharmacoat® 603, Methocel® E3, Methocel® E5, Methocel® E6 y sus mezclas. El polímero hidrófilo del subrecubrimiento osmótico puede estar presente en una cantidad entre 1 % y 30 % en peso de la composición del subrecubrimiento osmótico. Por ejemplo, en ciertas realizaciones el polímero hidrófilo está presente en una cantidad entre 1 % y 20 %, en otras realizaciones entre 3 % y 10 % y aún en otras realizaciones en 7 % en peso de la composición del subrecubrimiento osmótico.

En al menos una realización, el subrecubrimiento osmótico comprende 7 % de Pharmacoat® 606, 1 % de cloruro de sodio y 92 % de agua, en peso de la composición del subrecubrimiento osmótico.

Un método para producir el subrecubrimiento osmótico puede ser el siguiente. El al menos un agente osmótico, por ejemplo cloruro de sodio, se disuelve en agua. La solución de agente osmótico y agua se calienta después a 60°C. Después se agrega gradualmente el polímero hidrófilo a la solución. Se puede usar un agitador magnético para ayudar a mezclar el polímero hidrófilo con la solución del agente osmótico y agua. La solución de subrecubrimiento osmótico resultante se puede usar a continuación para recubrir el núcleo de la forma farmacéutica osmótica en un granulador de lecho fluidizado, como un granulador fabricado por Glatt (Alemania) o Aeromatic (Suiza) hasta el aumento de peso deseado. Una temperatura de entrada entre 10°C y 70°C, preferentemente entre 30°C y 55°C, y más preferentemente entre 40° C y 45° C; una temperatura de salida entre 10°C y 70°C, preferentemente entre 20°C y 45°C, y más preferentemente entre 30°C y 35°C; una temperatura del producto entre 10°C y 70°C, preferentemente entre 20°C y 45°C, y más preferentemente entre 30°C y 35°C; un flujo de aire entre 10 m^3/h y 180 m^3/h, preferentemente entre 40 m^3/h y 120 m^3/h y más preferentemente entre 60 m^3/h y 80 m^3/h; una presión de pulverización entre 0,5 bar y 4,5 bar, preferentemente entre 1 bar y 3 bar y más preferentemente de 2 bar; una temperatura de curado entre 10°C y 70°C, preferentemente entre 20°C y 50°C y más preferentemente entre 30°C y 40°C; y un tiempo de curado entre 5 minutos y 720 minutos; preferentemente entre 10 minutos y 120 minutos y más preferentemente de 30 minutos. También se puede usar cualquier otra tecnología que dé como resultado la formulación de recubrimiento del subrecubrimiento osmótico compatible con los objetivos de la invención.

La relación de los componentes en el núcleo, la membrana semipermeable y/o la membrana soluble en agua y/o al menos un recubrimiento de control de la liberación y/o subrecubrimiento osmótico así como la cantidad de las diversas membranas o recubrimientos aplicados se puede

variar para controlar la administración de la sal de bupropion ya sea predominantemente mediante difusión a través de la superficie de la membrana semipermeable o predominantemente mediante bombeo osmótico a través de al menos un pasadizo en la membrana semipermeable, y combinaciones de éstos de modo que la forma farmacéutica pueda presentar un perfil de liberación modificada, liberación controlada, liberación sostenida, liberación extendida, liberación prolongada, liberación bifásica, liberación retardada o una combinación de los perfiles de liberación por lo cual la velocidad de liberación in vitro de la sal de bupropion es tal que después de 2 horas se libera de 0 % a 20 % en peso de la sal de bupropion, después que 4 horas se libera de 15 % a 45 % en peso de la sal de bupropion, después de 8 horas, se libera de 40 % a 90 % en peso de la sal de bupropion y después de 16 horas, se libera más de 80 % en peso de la sal de bupropion. En las realizaciones en las que el modo de salida de la sal de bupropion comprende numerosos poros, la cantidad de formador de poros empleada para lograr las velocidades de disolución in vitro deseadas puede ser determinada fácilmente por los técnicos con experiencia en área de administración de fármacos.

En al menos una realización el núcleo de la forma farmacéutica osmótica comprende bromhidrato de bupropion. La proporción de bromhidrato de bupropion en el núcleo puede ser de 40 % a 99 %, como por ejemplo de 40 %, 45 %, 50 %, 55 %, 60 %, 65 %, 70 %, 75 %, 80 %, 85 %, 90 %, 95 % o 99 % del peso seco del núcleo.

En ciertas realizaciones, el núcleo de la forma farmacéutica osmótica comprende al menos un medio para aumentar la presión hidrostática dentro de la membrana o el recubrimiento. La membrana o el recubrimiento pueden ser una membrana semipermeable, un recubrimiento de control de la liberación, un recubrimiento soluble en agua, un subrecubrimiento osmótico o cualquiera de sus combinaciones. El núcleo de la forma farmacéutica osmótica tiene una presión osmótica eficaz mayor que la del líquido circundante en el ambiente de uso para que haya una fuerza conductora neta para que el agua penetre en el núcleo. El al menos un medio para aumentar la presión hidrostática dentro de la membrana o

recubrimiento puede ser cualquier material que aumente la presión osmótica del núcleo de la forma farmacéutica osmótica. El al menos un medio para aumentar la presión hidrostática dentro de la membrana o recubrimiento puede ser, por ejemplo, la sal de bupropion, un osmoagente, cualquier material que pueda interactuar con agua y/o un líquido biológico acuoso, hincharse y retener agua dentro de su estructura, como por ejemplo un osmopolímero y cualquiera de sus combinaciones. El osmoagente puede ser soluble o hinchable. Los ejemplos de solutos osmóticamente eficaces son sales y azúcares inorgánicos y orgánicos. La sal de bupropion en sí misma puede ser un osmoagente o se puede combinar con uno o más de otros osmoagentes, como por ejemplo, sulfato de magnesio, cloruro de magnesio, cloruro de sodio, cloruro de litio, sulfato de potasio, carbonato de sodio, sulfito de sodio, sulfato de litio, cloruro de potasio, carbonato de calcio, sulfato de sodio, sulfato de calcio, fosfato ácido de potasio, lactato de calcio, d-manitol, urea, inositol, succinato de magnesio, ácido tartárico, ácidos solubles 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 arábiga, goma ghatti, goma karaya, goma de algarrobo, pectina, almidón y sus mezclas. En ciertas realizaciones la cantidad de osmoagente puede ser, por ejemplo, de 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90 ó 95% del peso seco del núcleo.

El osmoagente útil en ciertas realizaciones de la presente invención puede ser cualquier agente que pueda generar un gradiente de presión osmótica para el transporte de agua desde el ambiente externo de uso a la forma farmacéutica osmótica. Los osmoagentes también se conocen como compuestos osmóticamente eficaces, solutos osmóticos y agentes de imbibición de líquidos osmóticos. Los osmoagentes útiles en ciertas realizaciones de la presente invención son solubles en líquidos acuosos y biológicos, como los compuestos ionizantes, los compuestos intrínsecamente polares, los ácidos inorgánicos, los ácidos orgánicos, las bases y las sales. En al menos una realización el osmoagente es un sólido y se disuelve para formar una solución con los líquidos

embebidos en la forma farmacéutica osmótica. Se puede usar una amplia gama de osmoagentes para proporcionar el gradiente de presión osmótica usado para mover la sal de bupropion desde el núcleo de la forma farmacéutica osmótica. Los ejemplos de sales inorgánicas útiles 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 ácido de potasio, cloruro de sodio, sulfato de sodio, fosfato de sodio, sulfito de sodio, nitrato de sodio, nitrito de sodio y sus mezclas. Los ejemplos de sales de ácidos orgánicos útiles como osmoagentes incluyen citrato de sodio, tartrato ácido de potasio, bitartrato de potasio, bitartrato de sodio y sus mezclas. Los ejemplos de ácidos sólidos ionizables útiles como osmoagentes incluyen ácidos tartárico, cítrico, maleico, málico, fumárico, tartrónico, itacónico, adípico, succínico, mesacónico y sus mezclas. Los ejemplos de otros compuestos útiles 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 éstos. En al menos una realización el osmoagente se selecciona entre cloruro de sodio, bromuro de sodio, bisulfato de sodio, tartrato ácido de potasio, ácido cítrico, manitol, sacarosa y sus mezclas. Las combinaciones de estos osmoagentes son permisibles. El osmoagente puede estar presente en una cantidad entre 0,1 % y 50 % del peso de la forma farmacéutica. Por ejemplo, en ciertas realizaciones el osmoagente está presente en una cantidad entre 1 % y 40 %, y en otras realizaciones entre 1 % y 20 % del peso de la forma farmacéutica.

En ciertas realizaciones, el al menos un medio para aumentar la presión hidrostática puede comprender, además de un osmoagente, cualquier material que pueda interactuar con agua y/o un líquido biológico acuoso, hincharse y retener agua dentro de su estructura. En ciertas realizaciones el al menos un medio para aumentar la presión hidrostática es un osmopolímero, que puede ser ligeramente reticulado o no reticulado. Los polímeros no

reticulados que se van a usar como osmopolímeros, cuando están en contacto con agua y/o líquidos biológicos acuosos, no se deben disolver en agua, manteniendo por consiguiente su integridad física. Dichos polímeros se pueden elegir, por ejemplo, entre el grupo de los derivados del ácido acrílico (p. ej., poliacrilatos, poli-metacrilato de metilo, poli ésteres de alquilos superiores del (ácido acrílico), 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 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 acrílicas; poliacrilamidas, poli(metacrilato de hidroxi etilo), poli(alcohol vinílico), poli(óxido de etileno), poli N-vinil-2-pirrolidona, resinas de origen natural como polisacáridos (p. ej., dextranos, gomas solubles en agua, almidones, almidones modificados químicamente), derivados de celulosa (p. ej., ésteres de celulosa, éteres de celulosa, celulosa modificada químicamente, celulosa microcristalina, carboximetilcelulosa y metilcelulosa sódicas), almidones.

En ciertas realizaciones, el núcleo de la forma farmacéutica osmótica comprende además un medio para dispensar forzadamente la sal de bupropion desde el núcleo hacia el exterior de la forma farmacéutica. El al menos un medio para dispensar forzadamente la sal de bupropion puede ser cualquier material que se pueda hinchar en agua y/o líquidos biológicos acuosos y retener una fracción significativa de agua dentro de su estructura, y que no se disuelva en agua y/o líquidos biológicos acuosos, un medio para generar un gas, un soluto osmóticamente eficaz o cualquier combinación de éstos el cual puede estar opcionalmente rodeado por una membrana o 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 de bupropion, el gas y los compuestos y que sea permeable al pasaje de agua y/o líquidos biológicos acuosos. Dicho recubrimiento o membrana comprende, por ejemplo, una membrana semipermeable, una membrana microporosa, una membrana asimétrica, donde la membrana asimétrica puede ser permeable, semipermeable, perforada o no perforada. En al menos una realización, el al menos un medio para dispensar forzadamente la sal de bupropion desde el núcleo de la forma farmacéutica osmótica comprende un medio para generar gas, donde el medio para generar gas está rodeado, por ejemplo, por una membrana semipermeable. En funcionamiento, cuando el medio que genera gas se embebe de agua y/o líquidos biológicos acuosos, el medio para generar gas reacciona y genera gas, aumentando de tamaño y expandiendo así el al menos un medio para dispensar forzadamente la sal de bupropion unidireccional o multidireccionalmente. El medio para generar un gas comprende cualquier compuesto o compuestos, que puedan producir efervescencia, como por ejemplo, al menos un compuesto sólido ácido y al menos un compuesto sólido básico, que en presencia de un líquido pueden reaccionar para formar un gas, como por ejemplo, dióxido de carbono. Los ejemplos de compuestos ácidos incluyen, ácidos orgánicos como málico, fumárico, tartárico, itacónico, maleico, cítrico, adípico, succínico y mesacónico y ácidos inorgánicos como sulfámico o fosfórico, también sales ácidas como citrato monosódico, tartrato ácido de potasio y bitartrato de potasio. Los compuestos básicos incluyen, por ejemplo, sales metálicas de carbonatos y bicarbonatos, como los carbonatos y bicarbonatos de metales alcalinos. Los materiales ácidos y básicos se pueden usar en cualquier proporción conveniente entre 1 y 200 partes del al menos un compuesto ácido a al menos un compuesto básico o 1 a 200 partes del al menos un compuesto básico a al menos un compuesto ácido. El medio para generar gas, se describe por ejemplo en la patente de los EE.UU. N° 4,235,236.

En al menos una realización, el al menos un medio para dispensar forzadamente la sal de bupropion desde el núcleo de la forma farmacéutica osmótica comprende cualquier material que se pueda hinchar en agua y/o líquidos biológicos acuosos y retener una fracción

importante de agua dentro de su estructura, y que no se disuelva en agua y/o líquidos biológicos acuosos, como por ejemplo, un hidrogel. Los hidrogeles incluyen, por ejemplo, polímeros hidrófilos ligeramente reticulados, que se hinchan en alto grado en presencia de líquidos sin disolverse, y que generalmente presentan un aumento de volumen de 5 a 50 veces. Los ejemplos de hidrogeles incluyen poli(metacrilatos de hidroxialquilos), poli(acrilamida), poli(metacrilamida), poli(N-vinil-2-pirrolidona), hidrogeles aniónicos y catiónicos, complejos polielectrolíticos, un copolímero insoluble en agua, hinchable en agua producido formando una dispersión de copolímeros finamente divididos de anhídrido maleico con estireno, etileno, propileno, butileno o isobutileno reticulados con de 0,001 a 0,5 moles de un reticulador poliinsaturado por mol de anhídrido maleico en el copolímero según se divulga en la patente de los EE.UU. N° 3,989,586, los polímeros hinchables en agua o N-vinil lactamas como las divulgadas en la patente de los EE.UU. N° 3,992,652, poli(vinil pirrolidona)semi sólida reticulada, hidrogeles de diésteres de poliglucano reticulado como los divulgados en la patente de los EE.UU. N° 4,002,173, los hidrogeles aniónicos de monómeros N-vinil heterocíclicos como los divulgados en la patente de los EE.UU. N° 4,036,788, los geles hidrófilos ionogénicos como los descritos en J. Biomedical Mater, Res., Vol. 7, páginas 123 a 126, 1973, y similares. Algunos de los osmopolímeros e hidrogeles son intercambiables. Dicho medio puede opcionalmente estar cubierto por una membrana o recubrimiento impermeable al pasaje de la sal de bupropion y los compuestos y permeable al pasaje de agua y/o líquidos biológicos acuosos. Dicho recubrimiento o membrana comprende, por ejemplo, una membrana semipermeable, una membrana microporosa, una membrana asimétrica, donde la membrana asimétrica puede ser permeable, semipermeable, perforada o no perforada.

En al menos otra realización, el al menos un medio para dispensar forzadamente la sal de bupropion del núcleo de la forma farmacéutica osmótica comprende al menos un soluto osmóticamente eficaz rodeado por una membrana o recubrimiento impermeable al pasaje de la sal de bupropion y los compuestos y permeable al pasaje de agua

y/o líquidos biológicos acuosos tal que el soluto osmóticamente eficaz presenta un gradiente de presión osmótica a través de una membrana o recubrimiento. Dicho recubrimiento o membrana comprende, por ejemplo, una membrana semipermeable, una membrana microporosa, una membrana asimétrica, donde la membrana asimétrica puede ser permeable, semipermeable, perforada o no perforada. Los solutos osmóticamente eficaces incluyen, por ejemplo, los osmoagentes descritos antes.

En las realizaciones de la forma farmacéutica osmótica en las que el medio para dispensar forzadamente la sal de bupropion está rodeado por una membrana o recubrimiento, se puede agregar al menos un plastificante a la composición de la membrana para impartir flexibilidad y elasticidad a la membrana o recubrimiento. En las realizaciones donde el medio para dispensar forzadamente la sal de bupropion comprende un medio para generar un gas, la membrana o recubrimiento deben ser elásticos para evitar la ruptura de la membrana o recubrimiento durante el período de administración de la sal de bupropion. La patente de los EE.UU. N° 4,235,236 describe la fabricación de dicha membrana o recubrimiento. Los plastificantes, que se pueden usar en estas realizaciones incluyen, por ejemplo, plastificantes cíclicos y acíclicos, ftalatos, fosfatos, citratos, adipatos, tartratos, sebacatos, succinatos, glicolatos, glicerolatos, benzoatos, miristatos, sulfonamidas halogenadas fenilos, poli(alquilenglicoles), poli(alquilendioles), poliésteres de alquilenglicoles, ftalatos de dialquilo, ftalatos de dicicloalquilo, ftalatos diarilo y ftalatos de alquilo-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 alquilo y arilo, como por ejemplo, fosfato de tributilo, fosfato de trioctilo, fosfato de tricresilo, fosfato de trioctilo, fosfato de tricresilo y fosfato de trifenilo; citrato de alquilo y ésteres de citrato como citrato de tributilo, citrato de trietilo y acetil trietil citrato; adipatos de alquilo, 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 alquilo, como por ejemplo, sebacato de dietilo, sebacato de dipropilo y sebacato de dinonilo; succinatos de alquilo, como por ejemplo, succinato de dietilo y succinato de dibutilo; glicolatos de alquilo, glicerolatos de alquilo, esteres de glicol y ésteres de glicerol, como por ejemplo, diacetato de glicerol, triacetato de glicerol, monolactato diacetato de glicerol, metil ftalil etil glicolato, butil ftalil butil glicolato, diacetato de etilenglicol, dibutirato de etilenglicol, diacetato de trietilenglicol, dibutirato de trietilenglicol, dipropionato de trietilenglicol y sus mezclas. 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 de bupropion desde el núcleo de ciertas realizaciones de la forma farmacéutica osmótica se pueden ubicar de modo tal que esté ubicado aproximadamente en el centro dentro del núcleo de la forma farmacéutica osmótica y esté rodeado por una capa que comprenda la sal de bupropion. Dicha configuración se divulga en la patente de EE.UU. N° 6,352,721. Alternativamente, el núcleo de la forma farmacéutica osmótica comprende al menos dos capas en las cuales la primera capa comprende la sal de bupropion, el osmoagente y/o el osmopolímero y opcionalmente al menos un excipiente farmacéuticamente aceptable adyacente a una segunda capa que comprende el medio para dispensar forzadamente la sal de bupropion. Alternativamente, el núcleo de la forma farmacéutica osmótica comprende una estructura multicapa en la cual la capa que comprende la sal de bupropion está ubicada entre dos capas del medio para dispensar forzadamente la sal de bupropion desde la forma farmacéutica osmótica.

Combinaciones

La presente invención también contempla las combinaciones de la sal de bupropion con al menos otro fármaco. Por ejemplo, se proporciona una composición que comprende un primer componente de bromhidrato de bupropion y un segundo componente de al menos otro fármaco, donde los dos componentes están presentes en una cantidad eficaz para el tratamiento de una afección. La presente

invención proporciona además un método 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 fármaco. Los técnicos con experiencia sabrán o podrán determinar por métodos conocidos qué combinaciones de fármacos son aceptables. Los tipos de fármacos que se pueden seleccionar como el segundo fármaco incluyen a modo de ejemplo antidepresivos, ansiolíticos, antiinflamatorios esteroideos y no esteroideos, ISRS, antijaquecosos, analgésicos, antieméticos, fármacos para tratar el abuso como de la nicotina, moduladores del apetito, anti virales, vasodilatadores, analgésicos, et al. Por ejemplo, el otro fármaco puede ser un antidepresivo seleccionado entre: inhibidores de la monoamino oxidasa (MAO), antidepresivos tricíclicos, inhibidores de la recaptación de serotonina, inhibidores selectivos de la recaptación de norepinefrina (ISRN), aminocetonas, antagonistas de la serotonina, inhibidores de la recaptación de dopamina, inhibidores de la recaptación dual, potenciadores de la norepinefrina, potenciadores de la actividad de la serotonina, potenciadores de la actividad de la dopamina y sus combinaciones. Los ejemplos de otros fármacos que se pueden combinar con bromhidrato de bupropion incluyen citalopram, escitalopram, venlafaxina, clozapina, melperona, amperozida, iloperidona, risperidona, quetiapina, olanzapina, ziprasidona, aripiprazol, reboxetina, Viagra®, sertralina, paroxetina, fluoxetina, gabapentina, ácido valproico, amitriptilina, lofepramina, fluvoxamina, imipramina, mirtazapina, nefazodona, nortriptilina, SAM-E y sus combinaciones. En al menos una realización, se proporciona una combinación de bromhidrato de bupropion y citalopram. En al menos otra realización, se proporciona una combinación de bromhidrato de bupropion y escitalopram. En al menos otra realización se proporciona una combinación de bromhidrato de bupropion y venlafaxina.

En ciertas realizaciones, los productos de combinación se pueden hacer proporcionando un sobre recubrimiento para prácticamente rodear el recubrimiento de control de la liberación de cada micropartícula. En ciertas realizaciones, se logra una liberación pulsátil de al

menos otro fármaco desde las micropartículas recubiertas. Este sobre recubrimiento puede ser un sobre recubrimiento de liberación inmediata que incluya al menos otro fármaco y al menos un polímero hidrófilo de baja viscosidad. El polímero de baja viscosidad asegura la liberación inmediata del otro fármaco desde el sobre recubrimiento. En al menos una realización, el polímero de baja viscosidad usado en el sobre recubrimiento es hidroxipropilmetilcelulosa (HPMC). El sobre recubrimiento también puede incluir un lubricante como talco. Como tal, esta realización puede proporcionar una liberación inmediata de al menos otro fármaco desde el sobre recubrimiento en una primera fase de liberación del fármaco, y luego la subsiguiente liberación controlada del bromhidrato de bupropion desde la micropartícula recubierta con el recubrimiento de control de la liberación en una segunda fase de liberación del fármaco.

Además, se pueden combinar en una forma farmacéutica combinaciones de micropartículas de la invención cada uno con un recubrimiento funcional diferente. Por ejemplo, combinando un primer grupo de micropartículas recubiertas sin recubrimiento que enmascare el sabor ni recubrimiento entérico con un segundo grupo de micropartículas recubiertas con recubrimiento de liberación sostenida o retardada, se puede lograr un perfil de liberación del fármaco pulsátil o cronoterapéutico, (consulte, por ejemplo, US 5,260,068, US 6,270,805, US 6,926,909, US2002/0098232, US2004/0197405, US 6,635,284, o US 6,228,398).

En otras realizaciones, la combinación puede comprender al menos 2 micropartículas diferentes una de las cuales contiene bromhidrato de bupropion y la otra el segundo fármaco las que están contenidas en una formulación en cápsula.

Si bien sólo se trataron combinaciones específicas de las diversas características y componentes de la presente invención, será evidente para los técnicos con experiencia en el área, que se pueden utilizar subconjuntos deseados de las características y componentes divulgados y/o combinaciones alternativas de estas características y componentes según se desee.

Como se verá en los ejemplos no limitantes que se describen más adelante, los recubrimientos de la invención son muy versátiles. Por ejemplo, la duración y el tiempo del período de retraso se pueden controlar mediante la velocidad de hidratación y el espesor del recubrimiento de liberación modificada. Por lo tanto, es posible regular la velocidad de hidratación y la permeabilidad del recubrimiento de control de la liberación para que se pueda lograr el perfil de liberación controlada deseado. No se prefiere ningún espesor en particular para el recubrimiento de control de la liberación, ya que éste dependerá del perfil de liberación controlada deseado. Otros parámetros en combinación con el espesor del recubrimiento de control de la liberación incluyen variar las concentraciones de uno o más de los ingredientes de la composición del recubrimiento de control de la liberación, variar la temperatura de curado y la duración del curado de las micropartículas del comprimido recubierto y, en ciertas realizaciones, variar el nivel de agente osmótico. El técnico con experiencia sabrá qué parámetros o combinaciones de parámetros cambiar para lograr un perfil de liberación controlada deseado.

4. ESTUDIOS DE ESTABILIDAD

La estabilidad mejorada del bromhidrato de bupropion, en particular en comparación con el bupropion HCl, es claramente evidente a partir de los estudios de degradación realizados sobre el ingrediente farmacéutico activo (IFA), solo, en presencia de excipientes y en forma de comprimidos XL. Los resultados se describen más detalladamente en los ejemplos siguientes.

Las expresiones "estabilidad mejorada", "mayor estabilidad", "estabilidad aumentada" o "más estable" como se usan aquí significan que la sal de bupropion (bromhidrato de bupropion) y las composiciones, las formulaciones o los medicamentos que contienen la sal de bupropion, cuando se exponen a condiciones similares, es decir, cuando se almacenan durante al menos 3, 4, 5 y/o al menos 6 meses en condiciones de almacenamiento acelerado (es decir, 40 grados C a 75 % de humedad relativa, presentan menos degradación según se determina

por la formación de al menos un producto de degradación característico de la degradación de bupropion y/o la retención de la concentración, en comparación con otras composiciones, por lo demás similares, que contienen clorhidrato de bupropion. Esto incluye en particular, composiciones que contienen bromhidrato de bupropion que presentan menos degradación basada en una cantidad menor de al menos un compuesto característico de la degradación del bupropion en relación con una composición, por lo demás similar, de clorhidrato de bupropion almacenada en condiciones de almacenamiento acelerado similares es decir, 40 grados C a 75 % de humedad durante al menos 3 meses, 4 meses, 5 meses y/o al menos 6 meses. Además otro indicador de la estabilidad mejorada es que la composición de bupropion HBr presenta menos fluctuación en un perfil de disolución in vitro que muestra menos fluctuación en relación con una composición, por lo demás similar, de bupropion HCl después del almacenamiento prolongado en condiciones similares y donde la disolución se analiza en condiciones similares (medio y tiempo) en particular después de haber sido almacenadas durante al menos 3 meses, 4 meses, 5 meses y/o al menos 6 meses a 40 grados C y 75 % de humedad relativa.

"Menos degradación" significa cualquier disminución cuantificable en la cantidad de al menos una impureza o producto de degradación característico de la degradación de bupropion o cualquier diferencia cuantificable (mejora de la fluctuación o fluctuación reducida) en la retención de la concentración en relación con una composición, por lo demás similar, de bupropion HCl después de que las composiciones fueron almacenadas por tiempos prolongados, es decir, durante al menos 3 meses, 4 meses, 5 meses y/o 6 meses a 40 grados C y 75 % de humedad relativa. Los "productos de degradación" incluyen los enumerados en la página 281 de la 26ª edición de la USP y todos los otros productos de degradación que puedan aparecer como picos en un cromatograma durante la determinación del contenido. Un indicador de mejor retención de la concentración es una composición de bupropion HBr que presenta menos fluctuación en el perfil de disolución después del almacenamiento prolongado, es decir al menos 3, 4, 5 ó 6 meses a 40 grados C y 75 % de humedad relativa en relación con una composición, por lo demás

similar, de bupropion HCl analizada en condiciones de disolución similares.

Se llevó a cabo una comparación de la estabilidad de varias sales de bupropion, incluidas las sales de HBr, HCl, maleato, tosilato, fumarato, succinato, tartrato y citrato, colocando estas sales en viales tanto abiertos como cerrados en una cámara de estabilidad mantenida a 40 grados C y 75 % de humedad relativa durante diversos períodos. Se evaluó la estabilidad de las sales basándose en la formación de los productos de degradación principales (ver más adelante) según se determinó por el análisis de HPLC y de determinación de la concentración en % (o contenido) del IFA, después de períodos específicos en la cámara de estabilidad. También se estudió el efecto de la adición de disolventes, como agua, etanol y alcohol isopropílico.

Los resultados indican inequívocamente que después de al menos 3 meses o después de al menos 6 meses la sal de HBr de bupropion, en promedio, fue la que mostró menor cantidad de productos de degradación y retuvo la actividad más alta de todas las sales probadas. En consecuencia la sal de HBr posee la mayor estabilidad. Estos resultados son inesperados y no podrían ser previstos de ninguna manera por un experto en el área puesto que ninguna de las otras sales probadas mostró tener esta estabilidad mejorada.

Se realizaron otras pruebas de estabilidad comparando directamente las sales de bupropion HBr y de bupropion HCl en estudios de degradación forzada. Estos estudios se llevaron a cabo en frascos cerrados en una cámara de estabilidad mantenida a 40 grados C y 75 % de humedad relativa. A los tiempos especificados, se analizó el material de los frascos para determinar la presencia de productos de degradación y la concentración en % (contenido en %). Se encontró inesperadamente que la cantidad de impurezas fue sistemáticamente inferior y la concentración en % fue sistemáticamente mayor para la sal de HBr en comparación con la sal de HCl.

También se llevaron a cabo estudios de degradación forzada sobre los IFA bupropion HBr y bupropion HCl en

presencia de los excipientes corrientes utilizados en las formulaciones farmacéuticas. Se observó la cantidad de los productos de degradación principales 24 y 48 horas después del tratamiento a 55°C, a 55°C y 100 % de humedad relativa y a 105 grados C. Una vez más, se encontró inesperadamente que la sal de HBr fue la que mostró la menor degradación (de acuerdo con lo determinado por la formación de impurezas) en estas condiciones.

También se comparó la estabilidad de las formulaciones en comprimidos de sales de bupropion HCl y HBr. Para ambas sales, se evaluaron un comprimido que tenía el primer recubrimiento de control de la liberación (EC) así como un comprimido con doble recubrimiento (con un recubrimiento de control de la liberación y un recubrimiento de barrera contra la humedad). Los comprimidos se colocaron individualmente en un vidrio de reloj sin tapar, y se expusieron a las condiciones aceleradas de 40°C y 75 % de humedad relativa en una cámara de estabilidad. Después de 13 y 20 días, se determinó el contenido de las muestras y se realizó el análisis de impurezas.

Para el comprimido de bupropion HCl con un solo recubrimiento, el contenido de las impurezas de degradación principales 3-CBZ y 852U77 fue de 0,12 % y 0,38 % respectivamente, mientras que para los comprimidos de bupropion HBr, estos valores fueron 0,07 % y 0,49 %, respectivamente. Las otras impurezas de degradación y las impurezas desconocidas totales fueron muy similares en los dos productos; sin embargo, el valor del contenido para el producto de HBr fue mayor que para el de HCl. La diferencia en el contenido y en los niveles de impurezas resultó más importante en los comprimidos con doble recubrimiento. Para el mismo período del estudio el contenido de bupropion HCl fue menor (95,5 % en comparación con 98,6 % para el bupropion HBr) y el nivel de degradación y de impurezas desconocidas totales fue superior (3-CBZ: 0,28 %, 852U77: 1,23 %, 827U76: 0,10 % y totales 1,73 %) que para el bupropion HBr (3-CBZ: 0,12 %, 852U77: 0,41 %, 827U76: 0,05 % y totales 0,75 %).

Los estudios de estabilidad realizados aquí demostraron claramente la inesperada estabilidad mejorada del

buproprion HBr, en particular en comparación con el buproprion HCl, que se usa en todas las formas farmacéuticas disponibles en la actualidad. Esta estabilidad mejorada se observa en la forma de IFA solo, en la forma de IFA más excipientes y en los comprimidos de liberación extendida y de absorción mejorada. Por consiguiente las formulaciones farmacéuticas que comprenden bupropion HBr son no sólo nuevas, sino también inventivas debido a sus inesperadas y beneficiosas propiedades de estabilidad mejorada. Las formulaciones farmacéuticas que comprenden bupropion HBr mostrarán una mayor vida útil y resistirán el almacenamiento a temperaturas y niveles de humedad superiores en comparación con las formulaciones de bupropion HCl que se utilizan en la actualidad.

5. FORMAS POLIMÓRFICAS

Se sabe que las moléculas orgánicas pueden cristalizar en formas sólidas. Además, el mismo compuesto orgánico puede tener diferentes disposiciones cristalinas en la forma sólida, dependiendo de las condiciones en que se formó el producto cristalino. Este fenómeno se conoce comúnmente como polimorfismo. 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 instrumento RIGAKU miniflex (generador de radiación de Cu K$_\alpha$ de 30 KV, filtro de Ni) para obtener los datos de PXRD.

Se estableció un procedimiento estándar para generar bromhidrato de bupropion, este procedimiento estándar produce una primera forma polimórfica que se denominó forma polimórfica I. En la Figura 54 se muestra la PXRD relativa para la forma I y el perfil de calorimetría diferencial de barrido (DSC) se muestra en la Figura 55.

El bupropion HBr de la forma I se usó como materia de partida en experimentos para identificar otras formas polimórficas. Se identificaron otras dos formas polimórficas que se denominaron forma II y forma III. Las Figuras 56 y 57 muestran los datos de PXRD y el perfil de DSC, respectivamente, de la forma polimórfica II. Las

Figuras 58 y 59 muestran los datos de PXRD y el perfil de DSC, respectivamente, de la forma III.

La forma polimórfica II se obtuvo por recristalización de la forma I de disolventes o mezclas de disolventes como acetona-agua, metanol, diclorometano, tolueno-metanol y carbonato de dimetilo-metanol. La forma polimórfica III se obtuvo por recristalización de la forma polimórfica I en metanol. La Tabla 80 presenta una lista de condiciones de recristalización y la forma polimórfica que se obtiene en cada conjunto de condiciones.

Las tres formas polimórficas se sometieron a pruebas de estabilidad. Las muestras de las formas polimórficas se sometieron a las condiciones ICH (40° C, 75 % de H.R.) y se obtuvieron datos de PXRD a los 3 meses y 6 meses. Todas las muestras tuvieron el mismo perfil de PXRD lo que indica que esta forma polimórfica es estable en estas condiciones y no cambia ni se degrada. Las muestras de las formas polimórficas II y III se probaron después de 1 mes en las mismas condiciones aceleradas de estabilidad. La forma polimórfica II no mostró cambios en el perfil de PXRD mientras que el perfil de PXRD de la forma III mostró la conversión a la forma II. Estos datos sugieren que las formas polimórficas I y II son muy estables mientras que la forma polimórfica III no es tan estable como las formas I y II en las condiciones de prueba.

Las tablas 99 a 104 contienen ejemplos de comprimidos de bupropion HBr XL de 348 y 174 de acuerdo con la invención. La Tabla 105 contiene los datos de estabilidad para las formulaciones de bupropion HBr de ejemplo en las condiciones aceleradas para diferentes lotes durante diferentes periodos de tiempo.

Como se verá en los ejemplos no excluyentes que se describen más adelante, los recubrimientos usados en la presente invención son muy versátiles. Por ejemplo, la duración y el tiempo del período de retraso se pueden controlar mediante la velocidad de hidratación y el espesor del recubrimiento de liberación modificada. Otros parámetros 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 la invención descritas y/o la variación de la temperatura de curado y el periodo de curado de los núcleos de los comprimidos recubiertos. El técnico con experiencia sabrá qué parámetros o combinaciones de parámetros cambiar para lograr un perfil de liberación controlada deseado.

Los siguientes ejemplos ilustran la presente invención y de ningún modo pretenden limitar el alcance de la presente invención.

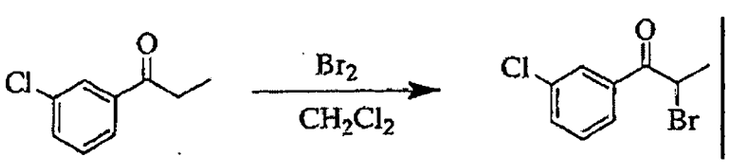
EJEMPLOS

EJEMPLO 1: PREPARACIÓN DE LA SAL DE BUPROPRION HBr

La sal de bupropion HBr se preparó de acuerdo con el método que se muestra en el esquema 1:

Esquema 1

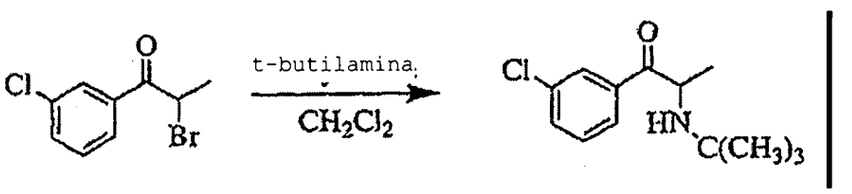
Reacción de bromación



3'-cloro-propiofenona PM = 168,62

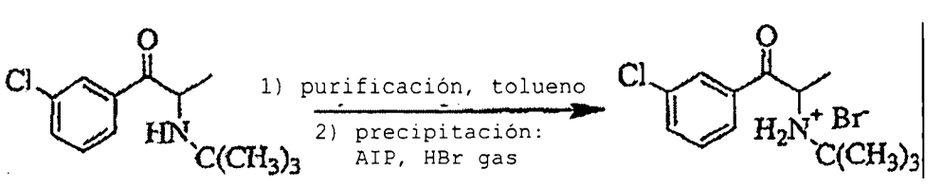
2-bromo-3'-cloro-propiofenona PM = 247,52

Reacción de aminación



2-t-butilamino-3'-cloro-propiofenona
PM = 239,75

Purificación / precipitación / secado



3) secado

704

Producto intermedio de bupropion HBr

Paso de finalización

Producto intermedio de bupropion HBr	Tamizado → Envasado	Bupropion .HBr producto final

(a) Reacciones de bromación y condensación

El material de partida 3'-cloro-propiofenona se bromó en cloruro de metileno por goteo de bromo en condiciones controladas. Al terminar la reacción se purificó el licor madre y después 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 terc-butilamina sustituye al átomo de bromo) forma la molécula final de bupropion. Después de la purificación del licor madre se obtuvo una solución de bupropion en tolueno. Se evaporó el disolvente y el bupropion se disolvió en isopropanol. Se precipitó el bromhidrato de la solución de isopropanol, con bromuro de hidrógeno gaseoso. Al terminar la precipitación, el producto se centrifugó, se lavó con isopropanol y se secó al vacío. Tras la aprobación de la descarga del secador, se descargó en tambores Kraft dentro de bolsas dobles de polietileno.

En el paso final, el intermediario anterior se tamizó para obtener el producto final que se empacó en tambores Kraft dentro de bolsas dobles de polietileno.

El análisis elemental del bupropion HBr se realizó con un analizador elemental Fisons EA 1108. Los resultados fueron compatibles con la fórmula molecular del bupropion HBr.

EJEMPLO 2: CARACTERIZACIÓN FISICOQUÍMICA DE LAS SALES DE BUPROPION

Se caracterizaron las siguientes sales de bupropion contra la sal de HCl:

ID del producto	Lote Núm.	Cantidad	Concentración (HPLC) determinada por R&D
Maleato de bupropion	030/018	100 g	99,7 %
Tosilato de bupropion	030/011/A	50 g	97,4 %
Fumarato de bupropion	031/1	10 g	89,8 %
Bupropion HBr	031/2	10 g	99,7 %
Succinato de bupropion	031/3	10 g	97,6 %
Tartrato ácido de bupropion	031/5	10 g	84,9 %
Tartrato neutro de bupropion	031/5B	10 g	51,7 %*
Citrato de bupropion	031/8	10 g	85,0 %

* no corregido por la concentración

Muestras de análisis térmico (DSC):

Se colocaron 2 a 5 mg de cada sal en recipientes de aluminio y se cubrieron con sus tapas. Se efectuó una DSC para cada muestra a una velocidad de 10° C/min (para la sal de HBr, se usaron velocidades diferentes para investigar los polimorfos) desde 30° C hasta 400° C. También se usó TGA para cada una de las sales de HBr, HCl, maleato y tosilato.

Resultados y discusión:

Datos fisicoquímicos:

A las ocho sales se les evaluó primero la pureza, el contenido de agua, el pH acuoso y los polimorfos posibles, mediante HPLC, KF, pH y DSC. Como se muestra en la Tabla 1, sólo las sales de maleato, tosilato, HBr y succinato fueron suficientemente puras, los contenidos de las otras estuvieron entre 51,7 % y 89,8 %.

Las sales se analizaron mediante DSC (a 10°C/min desde 30°C hasta 400°C) y también se midieron el pH (acuoso 0,5 %), y el contenido de humedad por KF. El TGA se realizó sobre las sales de HCl, maleato, tosilato y HBr.

Maleato: La DSC presentó un pico endotérmico de fusión a la temperatura de inicio de 199,1°C y un pico agudo más pequeño a 205°C. El contenido de humedad fue de 0,10 % y el pH de la solución acuosa al 0,5 % fue de 4,29.

Mediante recristalización en alcohol isopropílico (AIP)/EtOAc, el pico más pequeño desapareció casi por completo. El TGA mostró que este producto era térmicamente estable hasta al menos 150°C ya que se

observó una pérdida de peso de 1,3 % entre la temperatura ambiente y 100°C. Al igual que para el bupropion HCl, no se observó transición vítrea cuando se realizó un experimento de calentamiento-enfriamiento-calentamiento con el instrumento de TA.

Fumarato: La DSC presentó múltiples picos endotérmicos a diferentes temperaturas de inicio (172,3, 182,3, 202 y 217°C). El contenido de humedad fue de 0,09 % y el pH de la solución acuosa al 0,5 % fue de 3,84.

Tosilato: La DSC presentó un pico endotérmico de fusión a la temperatura de inicio de 150°C, un pico más pequeño a 90°C y múltiples picos a temperaturas mayores (> 200°C, probablemente de descomposición). El pico a 90°C se debió probablemente al disolvente acetato de isopropilo. El contenido de humedad fue de 1,71 % y el pH de la solución acuosa al 0,5 % fue de 5,56.

Mediante recristalización en acetonitrilo/hexano o acetonitrilo/EtOAc, el pico pequeño a 90°C desapareció, el contenido de humedad disminuyó a 0,23 %, y el pH cambió a 5,88. Después de dos meses, a la muestra recristalizada se le analizó nuevamente el contenido de humedad y se encontró que era de 0,18 %. Por lo tanto, hubo una diferencia entre la sal original y la recristalizada en términos de pureza y contenido de humedad (originalmente se pensó que estaba hidratada y/o era higroscópica).

El TGA mostró que este producto no era térmicamente estable ya que se observó una pérdida de peso de 1,3 % entre la temperatura ambiente y 100°C. Además la muestra dio un residuo de 10,3 % a 400°C en comparación con residuos mínimos para el bupropion HCl y el maleato. El experimento de calentamiento-enfriamiento-calentamiento se realizó en el instrumento de TA y mostró una transición vítrea (Tg) a 45°C. La Tg indica que la morfología es amorfa más que cristalina.

HBr: La DSC mostró un pico endotérmico de fusión a una temperatura de 224°C, con un hombro. La muestra se analizó a diferentes velocidades de barrido 1, 10, 15 y 20°C/min para buscar posibles polimorfos. No se

observaron diferencias importantes para la forma del pico endotérmico a diferentes velocidades de barrido. No se lograron mejorías ni mediante cristalización de la sal de HBr en diferentes disolventes ni mediante síntesis interna a partir de 3'-cloropropiofenona, en la forma del pico de fusión endotérmico a ~ 224°C (es decir, se mantuvo el mismo hombro a velocidades de 10°C o mayores). Se realizó un experimento de calentamiento-enfriamiento-calentamiento en el instrumento de TA y mostró una transición vítrea (Tg) a 23°C.

El contenido de humedad fue de 0,00 % y el pH de la solución acuosa al 0,5 % fue de 5,92.

Otras sales: Los resultados de la DSC de otras sales muestran múltiples picos endotérmicos de fusión. El pH y el contenido de agua de todas las sales se muestran en la Tabla 2.

En la Tabla 3 se presenta una comparación de la solubilidad y otras propiedades físicas del bupropion HBr frente al bupropion HCl.

Higroscopicidad del bupropion HBr:

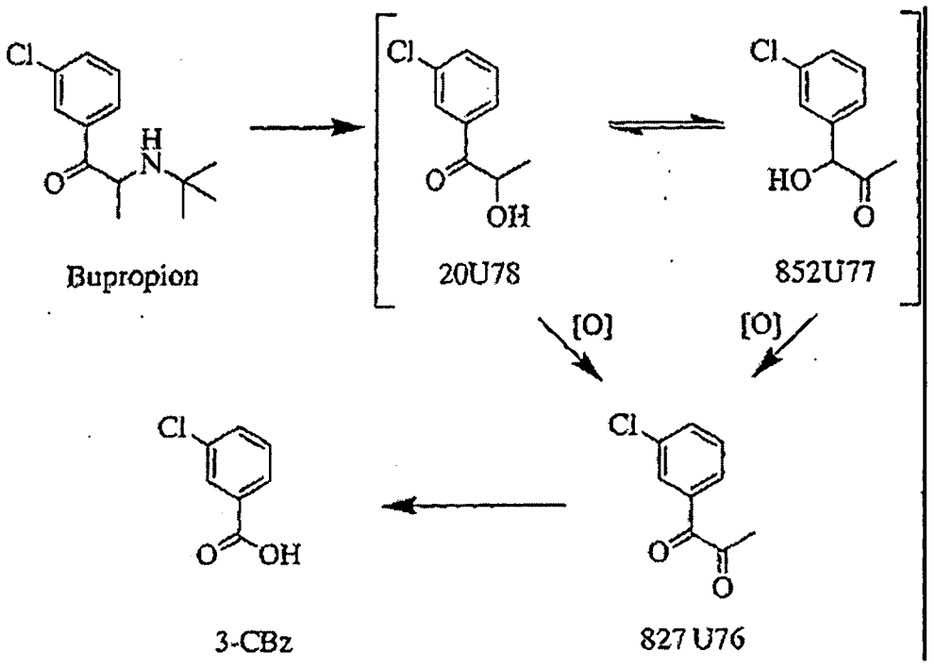
El análisis de sorción dinámica de vapor (DVS) del bupropion HBr sugiere que la muestra es un cristal anhidro y que tiene muy poca capacidad de incorporar agua (es decir, no es higroscópico). La muestra de bupropion HBr no presenta una incorporación significativa de agua en el intervalo de 0 % a 90 % de HR. La incorporación máxima de agua se midió a 0,14 % en peso a 90 % de HR. En la Figura 1 se muestra un perfil de DVS para el bupropion HBr y los datos de la isoterma de DVS para bupropion HBr se muestran en la Figura 2.

EJEMPLO 3: ESTUDIO DE ESTABILIDAD CON DEGRADACIÓN FORZADA

Las muestras de cada sal y las sales con agregado de cantidades conocidas de bupropion HCl XL se prepararon en las condiciones mencionadas en la Tabla 4. Las muestras se colocaron en la cámara de estabilidad a 40° C/75 % de HR, se sacaron a los 10, 20 y 32 días y se les determinó el contenido y las impurezas por HPLC. La estabilidad de las sales de bupropion se evaluó basándose en la formación del producto de degradación principal, el ácido

3-clorobenzoico (3-CBZ) y de los productos de degradación intermedios los derivados dicetona 827U76 y cetohidroxilo (20U78 y 852U77) (Esquema 2). El ácido 3-clorobenzoico se forma como resultado de la oxidación/hidrólisis del compuesto original, la sal de bupropion.

Esquema 2



Como ya se mencionó, las muestras de estabilidad se prepararon en viales de 2 mL y se usaron directamente para las determinaciones de contenido y análisis de impurezas por HPLC sin preparaciones adicionales de las muestras para minimizar los errores.

Los estudios de degradación forzada de 10 días sobre estas sales mostraron que el succinato, tartrato y citrato (mezclados o sin mezclar con los excipientes en viales cerrados) no fueron estables en las condiciones mencionadas en la Tabla 4. El contenido disminuyó sensiblemente, el nivel de impurezas conocidas y desconocidas aumentó y los colores de las sales cambiaron de los polvos blancos originales a productos amarillos semilíquidos. Por lo tanto, no se continuó estudiando estas sales.

Se continuó extrayendo muestras a los tiempos de muestreo de 10, 20 y 32 días para la estabilidad de las sales de maleato, tosilato, HBr y fumarato en paralelo con el

bupropion HCl. Los resultados se muestran en las Figuras 3 a 10. Los resultados de contenido e impurezas a los 20 días en viales cerrados para estas cinco sales se compararon con los de la sal más excipientes y se presentan en las Figuras 3 y 4. Las Figuras 5 a 7 presentan los resultados para las sales del fármaco (SF) mantenidas durante 32 días en viales cerrados y con agregado de cantidades conocidas de agua, agua-alcohol isopropílico (AIP)-etanol (EtOH) y AIP-EtOH.

Es de destacar que en los análisis en viales cerrados el contenido de impurezas (3-CBZ, 852U77 y totales) en la sal de HBr fue el más bajo en comparación con todas las demás sales incluida la de HCl (ver la Figura 3). Los niveles de 852U77 en las demás sales fueron comparables con los de HCl, sin embargo, los niveles de 3-CBZ y, en particular los niveles de impurezas totales fueron más altos en las demás sales que en la de HCl. En los resultados de determinación del contenido (concentración en %), el tosilato y las sales de HCl tuvieron una concentración similar después de 20 días en un vial cerrado (Figura 4). En el estudio de contenido, el orden de estabilidad para las sales de bupropion fue el siguiente: HBr>HCl≈tosilato>fumarato>maleato).

La estabilidad de las sales se evaluó después en condiciones más exigentes. A las sales del fármaco (SF) y los excipientes se les agregaron cantidades conocidas de agua, agua más EtOH y AIP, y EtOH y AIP. Como se puede ver en los resultados presentados en las Figuras 5 a 7, el orden de estabilidad (determinación del contenido) de las sales se puede resumir de la manera siguiente:

Estabilidad con agua: tosilato>maleato>HCl>HBr>
fumarato.

Estabilidad con AIP y EtOH: HCl>HBr>tosilato>maleato>
fumarato

Las sales de tosilato y maleato fueron más estables que las demás sales cuando fueron expuestas directamente al agua, y menos estables cuando fueron expuestas a los disolventes orgánicos AIP y EtOH.

Las sales de HCl y HBr fueron más estables que las demás sales cuando fueron expuestas directamente a AIP y EtOH y

menos estables con agua. La sal de fumarato no fue estable ni en agua ni en los disolventes orgánicos AIP y EtOH.

El nivel de las impurezas (conocidas, desconocidas y totales) varió en cada una de las sales en las condiciones de este experimento. El contenido de cada una de las impurezas principales (3CBZ y 52U77) y de las impurezas totales fue el siguiente (Figuras 8 a 10):

En agua, 3-CBZ: HCl>HBr ≈ maleato ≈ fumarato
852U77: fumarato>HBr>maleato>HCl
Imp. Totales: fumarato>HBr>HCl>tosilato>maleato

En AIP/EtOH: 3-CBZ: maleato>HBr>HCl>fumarato
852U77: fumarato>HBr≈HCl≈maleato≈tosilato
Imp. Totales: fumarato>maleato>HBr>HCl>tosilato

Basándose en los estudios de estabilidad de degradación forzada realizados sobre las sales de bupropion antedichas, se demostró que la estabilidad de oxalato, citrato, succinato y tartrato eran muy malas para la SF y la SF con agregado de cantidades conocidas (20 días: decoloración, bajo contenido y alto nivel de impurezas de degradación). Las sales de HBr, tosilato, maleato y en alguna medida la de fumarato son buenas candidatas para estudios posteriores. Entre estas últimas sales, la de HBr fue la mejor candidata debido a su estabilidad superior en un recipiente cerrado, al menor contenido de agua, a que no es higroscópica y es fácil de preparar.

La sal de tosilato también mostró buena estabilidad, aunque no fue tan pura como la de HBr, HCl o maleato. La sal de tosilato, sin embargo, no tiene un perfil de toxicidad aceptable.

También se encontró que la presencia de disolventes orgánicos como etanol y alcohol isopropílico tiene un impacto significativo sobre la estabilidad de estas sales.

EJEMPLO 4: ESTUDIOS COMPARATIVOS DE DEGRADACIÓN FORZADA SOBRE SALES DE IFA BUPROPION HCl Y BUPROPION HBr

La estabilidad de las sales de IFA bupropion HCl y bupropion HBr se evaluó adicionalmente en las condiciones aceleradas de 40°C/75 % de HR en una cámara de estabilidad. Las muestras se expusieron a las condiciones anteriores en un frasco cerrado durante algunos días y después se sometieron a análisis por HPLC. Las cantidades de los productos de degradación principales presentes después del tratamiento se compararon con las cantidades presentes al inicio.

Se pesaron por separado con exactitud cantidades de cada IFA en distintos frascos de vidrio ámbar de 50 mL como se muestra en la Tabla 5. Los frascos se cerraron y se colocaron en la cámara de estabilidad a 40°C/75 % de HR. Las muestras se analizaron después de 14 y 24 días (estudio I) y 10 días (estudio II), en forma cuantitativa mediante el tratamiento directo de todo el contenido del frasco de acuerdo con el método estándar de análisis por HPLC (P05.901.10).

Como se muestra en la Tabla 6, los productos de degradación resultantes en bupropion HCl y bupropion HBr fueron o bien similares o mejores para la sal de HBr.

El estudio anterior se repitió en dos lotes de cada uno de los IFA durante 10 días. Como se muestra en la Tabla 7, el nivel de impurezas en el caso de la sal de bupropion HBr fue menor que para la sal de bupropion HCl, además el valor de contenido para esta última fue menor que para la sal de HBr.

EJEMPLO 5: COMPRIMIDOS DE BUPROPION HBr DE LIBERACIÓN EXTENDIDA (XL)

El objetivo de este ejemplo fue describir el desarrollo de bupropion HBr XL (174 y 348 mg). Los procedimientos de granulación, formación de comprimidos y recubrimiento se describen detalladamente en este ejemplo. Se realizaron pruebas in vitro sobre los núcleos, los núcleos recubiertos con EC y los comprimidos con el recubrimiento final para determinar qué formulación daba los resultados deseados.

A partir de sus fórmulas estructurales, se observa que la diferencia entre las sales de bupropion HCl y bupropion

HBr es el anión. Esto, por supuesto, produce un peso molecular diferente. Sin embargo, estas diferencias se tomaron en cuenta en el presente estudio y se hicieron modificaciones a fin de obtener resultados de correlación in vitro con el bupropion HCl usando estudios de disolución.

Se observó previamente que cuando se analizó la liberación de bupropion HCl de 150 mg, el valor de base que se liberó fue de 130 mg. Sin embargo, cuando se analizó el bupropion HBr de 150 mg, el valor de base liberado fue sólo de 112 mg. De manera que se tuvo que aumentar la cantidad de bupropion HBr para aumentar el valor de base de 112 mg 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 - Proceso de granulación

En la Figura 11 se muestra un resumen del proceso de fabricación usado para la preparación de comprimidos de bupropion HBr XL.

Se usaron los materiales siguientes en la granulación de los núcleos de liberación inmediata de los comprimidos de bupropion HBr EA: bupropion HBr, alcohol polivinílico (PVA) y agua purificada. Una vez granulado, se agregó lubricante (Compritol 888) para completar la formulación.

Cada ensayo se dividió en 5 partes. El porcentaje de IFA en cada formulación fue de 93,75 %; el porcentaje de PVA en cada formulación fue de 3,125 %. En la Tabla 8 se describe un resumen del desglose de cada ensayo por parte.

El PVA se disolvió en agua purificada mediante un agitador magnético y se preparó una solución transparente e incolora.

Para granular el bupropion HBr en gránulos se usó el equipo de lecho fluido NIRO con la solución en PVA en un proceso conocido como amasado húmedo. La Figura 12 presenta un resumen del procedimiento de granulación.

El bupropion HBr se cargó en el lecho fluido y se inició la granulación. Las especificaciones usadas como pautas se muestran en la Tabla 9.

Se determinó la pérdida por secado después de cada granulación con el analizador de humedad. Se tomó una muestra de 1 g y se cargó en el analizador de humedad. La muestra se analizó durante 5 minutos a una temperatura de 105° C.

Después de completar la granulación de cada parte del lote, se combinaron las cinco partes. Se tamizaron a mano con un tamiz de malla núm. 14 (1,4 mm) y todos los granos más grandes se pasaron a través del Comil equipado con un tamiz de 2 mm.

Se usó Compritol 888 como lubricante en la formulación. Los gránulos de bupropion HBr tamizados y el Compritol 888 se cargaron en el mezclador en V y se mezclaron durante 5 minutos. El Compritol 888 constituyó 3,125 % de la formulación. El tamaño del lote final de gránulos se describe en la Tabla 10.

Bupropion HBr XL - Proceso de formación de comprimidos

Para preparar los comprimidos de bupropion HBr se usó la compresora Beta. Según 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 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 y 371,2 mg para los comprimidos de 348 mg. Se hicieron estos ajustes en el peso del comprimido para compensar el hecho de que se estaba usando bupropion HBr en lugar de bupropion HCl. Los pesos de los comprimidos individuales tuvieron un límite de control de ± 5 %, y el peso promedio de los comprimidos tuvo un límite de control de ± 3 % (usando diez comprimidos).

Se usó un durómetro para determinar la fuerza necesaria para romper diametralmente los comprimidos (fuerza de rotura por compresión) en dos mitades iguales. Un intervalo predeterminado, entre 6,0 y 12,0 SC, estableció las especificaciones de dureza para los comprimidos de 174 mg y 348 mg.

La friabilidad se determinó usando comprimidos que tenían en total un peso de 6,5 g en un friabilómetro durante 4 minutos a 25 rpm. Los comprimidos se desempolvaron antes y después de la prueba. Se usó como criterio una pérdida de peso menor que 0,8 % a fin de aceptar o rechazar el lote.

La Tabla 11 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 12 resume las especificaciones que se mantuvieron constantes durante la compresión de todos los lotes.

El diagrama de flujo que se muestra en la Figura 12 describe los pasos previos e incluye el proceso de formación de comprimidos. La Figura 13 presenta un resumen del procedimiento de formación de comprimidos.

Bupropion HBr XL - Proceso de recubrimiento

En la Figura 14 se muestra un resumen del proceso de recubrimiento usado para la preparación de comprimidos XL de bupropion HBr. El primer recubrimiento es de Ethocel y controla la liberación, al que sigue un recubrimiento final que actúa como barrera contra la humedad.

Para el recubrimiento de Ethocel y el recubrimiento final de los comprimidos XL de bupropion HBr, se usó el sistema O'Hara Labcoat II de 15 pulgadas. También se usaron una boquilla de pulverización y un mezclador de hélice.

Se desarrollaron varias soluciones de recubrimiento de Ethocel que se usaron para recubrir los comprimidos de bupropion HBr. La capa de recubrimiento de Ethocel se

colocó sobre los comprimidos que contenían una de las formulaciones que aparecen en la Tabla 13.

En la formulación 1, se combinaron alcohol etílico 95 % y AIP 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 el Ethocel y se dejó en agitación durante 30 minutos. Después, se agregó povidona a la solución y se mezcló durante toda la noche (15 a 20 horas).

En la formulación 2, se colocó PEG 4000 en un vaso de laboratorio con sebacato de dibutilo y se agitó hasta que se disolvieron. Se agregó alcohol etílico 95 % como se indica a fin de permitir la disolución total del PEG 4000. En un recipiente de acero inoxidable distinto se colocó el resto del alcohol etílico 95 % y se agregó el Ethocel con agitación y se agitó durante 30 minutos. A continuación, se agregó povidona y se dejó en agitación durante toda la noche (15 a 20 horas).

En la formulación 3, se colocó alcohol etílico 95 % en un recipiente de acero inoxidable. Mientras se agitaba se agregó PEG 4000 y se permitió que se disolviera. Una vez disuelto, se agregó el Ethocel y se dejó en agitación durante 30 minutos. Después, se agregó povidona a la solución y se mezcló durante toda la noche (15 a 20 horas).

Se desarrollaron dos soluciones de recubrimiento final y se usaron para recubrir los comprimidos de bupropion HBr después que habían sido recubiertos primero con el recubrimiento de Ethocel.

Una de las formulaciones siguientes que se muestran en la Tabla 14 se usó para recubrir los comprimidos con un recubrimiento final.

En la formulación A, se colocó el agua purificada en un vaso de vidrio de laboratorio y se le agregó Chroma-Tone DEB 5156-CLE y se dejó que se mezclara durante 15 minutos. El Eudragit se pasó a través de un tamiz de malla (núm. 60) antes de usar. Después de esto, se agregó

el Eudragit al vaso de laboratorio y se agitó durante 15 minutos más.

En la formulación B, se colocó la parte 1 del agua purificada en un vaso de vidrio de laboratorio y se le agregó PEG 4000 y se dejó que se mezclara hasta que se disolvió totalmente (5 minutos). Después se agregó citrato de trietilo y se dejó que se mezclara durante otros 5 minutos. Una vez disuelto, se agregó la solución a la suspensión de Eudragit y se dejó en agitación durante 45 minutos. El Eudragit se pasó a través de un tamiz de malla (n° 60) antes de usar. En otro vaso, se agregó la parte 2 del agua purificada al Syloid 244FP y se mezcló hasta que se disolvió por completo (10 minutos). Finalmente, la suspensión de Syloid se agregó a la suspensión de Eudragit y se dejó en agitación durante otros 10 minutos.

La Tabla 15 resume las especificaciones que se controlaron durante el proceso de recubrimiento con Ethocel y sus intervalos.

La Tabla 16 resume las especificaciones que se controlaron en el proceso de recubrimiento final y sus intervalos.

Estudios in vitro sobre los núcleos de bupropion HBr

Se realizó la prueba de disolución a los núcleos de bupropion HBr, a los diferentes aumentos de peso de los núcleos recubiertos con Ethocel y a los diferentes aumentos de peso de los comprimidos recubiertos con el recubrimiento final. Para realizar estos estudios se usó el método USP-1. La prueba de disolución se realizó usando 900 mL de HCl 0,1 N y a una velocidad de 75 rpm. Las muestras se tomaron cada hora durante 16 horas. Los perfiles de disolución se obtuvieron graficando el porcentaje acumulado de IFA disuelto en función de los tiempos de muestreo. Se mantuvieron las condiciones de sedimentación durante todos los experimentos.

En varios ensayos se utilizó el método USP-3 para realizar los estudios de disolución. Estas pruebas de disolución se realizaron durante 16 horas en total con el siguiente desglose: 2 horas usando 900 mL de líquido

gástrico simulado (LGS) de pH 1,2 con 0,5 % de lauril sulfato de sodio (LSS), seguido de 2 horas en 900 mL de solución amortiguadora de acetato de pH 4,5, seguido de 12 horas en 900 mL de líquido intestinal simulado (LIS) solución amortiguadora de fosfato de pH 6,8. Estos resultados se graficaron con los datos in vivo y los datos de bupropion HCl a fin de realizar una comparación.

Estudio sobre el lote [illegible]

[illegible] se granuló usando un equipo de lecho [illegible]. Después de terminar la granulación, el lote se pasó y antes de comprimir se agregó el lubricante (Compritol 888). La mezcla final se comprimió en forma de comprimidos de 348 mg con la compresora Beta con los punzones redondos cóncavos de 9 mm y 10 mm. La Tabla 17 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, si los hubiera, sobre la disolución (Figura 15). Se realizó una prueba de disolución a los núcleos de 348 mg a fin de determinar su liberación (Figura 16).

Los resultados de la granulación muestran que el tiempo de granulación promedio es de 2,0 horas y la LOD (pérdida por secado) promedio en % es de 0,345 %. Las Tablas 18 y 19 resumen los valores teóricos y reales de los parámetros que se controlaron en el proceso de compresión (usando los punzones de 9 mm y 10 mm, respectivamente).

[illegible] determinar la dureza de los comprimidos para [illegible] 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 3 kp, 6 a 7 kp y 9 a 10 kp cuyos perfiles de disolución se muestran en la Figura 15. Se observó que no hubo una diferencia significativa entre los tres intervalos de dureza diferentes.

Los perfiles de disolución de los núcleos de 348 mg (Figura 16) y 174 mg (Figura 17) mostraron que los

núcleos liberaron aproximadamente el 100 por ciento del IFA en una hora.

La disolución de los núcleos de 10 mm y 348 mg también se llevó a cabo para ver si la liberación de estos comprimidos era más rápida en comparación con la de los núcleos de 9 mm debido a su mayor área superficial (Figura 17).

Cuando se compararon los resultados de disolución de los núcleos de 9 mm y 10 mm (Figura 18), los núcleos de 10 mm no mostraron diferencias con respecto a los núcleos de 9 mm. Por lo tanto, los núcleos de 10 mm no se fabricaron ni se usaron más en este estudio.

Estudio sobre el lote BUP-HBr-XL-021-5

La formulación se granuló usando un equipo de lecho fluido NIRO. La mezcla final se comprimió en forma de comprimidos de 174 mg usando la compresora Beta con los punzones estándar, redondos, cóncavos de 7 mm de acero inoxidable. La Tabla 20 describe la cantidad de cada material en la granulación de los comprimidos de 174 mg. Es de destacar que los comprimidos de 348 y 174 mg tuvieron la misma composición y cantidad de cada material; la única variación fue el peso del comprimido, que se ajustó en la etapa de compresión. Se realizó una prueba de disolución a los núcleos de 174 mg para observar su liberación (Figura 19).

Los resultados de la granulación muestran que el tiempo de granulación promedio es de 2 horas con 6 minutos y la LOD promedio en % es de 0,26 %. La Tabla 21 resume los valores teóricos y reales de los parámetros que se controlaron en el proceso de compresión usando los punzones de 7 mm.

El perfil de disolución de los núcleos de 174 mg (Figura 19) mostró que los núcleos liberaron aproximadamente el 100 por ciento del IFA en una hora.

Estudio sobre el lote BUP-HBr-XL-348 mg-013-5

Usando los comprimidos de 348 mg, se pulverizaron un recubrimiento de Ethocel seguido de un recubrimiento

final sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 22.

Los parámetros son 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 flujo de suministro de aire: 200 CFW.

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 23 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 20) muestra que los comprimidos con un aumento de peso de 34 mg de recubrimiento de EC liberaron bupropion HBr más lentamente que los demás y que los comprimidos con un aumento de peso de 28 mg fueron los más rápidos para liberar el bupropion HBr en comparación con los otros aumentos de peso.

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 porcentaje de los sólidos en la solución se presentan en la Tabla 24.

Los parámetros 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 flujo de suministro de aire: 200 CFW.

Después de este ciclo del ensayo, no se volvió a usar Chroma-Tone debido a los problemas de formulación que causó. En primer lugar, limitaba la composición de la formulación debido a su falta de flexibilidad porque que no se podían variar las proporciones de Syloid, PEG y citrato de trietilo. En segundo lugar, la solución hacía espuma y coagulaba, lo que a su vez hacía que se tuviera

que cambiar el proceso de preparación de la solución de recubrimiento con respecto al original para que no volviera a coagular. Sin embargo, aún se puede considerar el Chroma-Tone como una opción para la formulación pero se deberán usar diferentes grados y hacer mezclas diferentes para adecuarse a los comprimidos de bupropion HBr XL.

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 25 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 21) muestra que los comprimidos con un aumento de peso de 7 mg de recubrimiento final fueron los de liberación más lenta 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-018-5

Usando los comprimidos de 348 mg, se pulverizaron un recubrimiento de Ethocel seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 26.

Los parámetros son 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 flujo de suministro 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 27 los pesos de los comprimidos a los 26 mg, 28 mg, 30 mg y 32 mg de aumento de peso.

La Figura 22 muestra que la velocidad de liberación de los comprimidos con aumentos de peso de 30 mg y 32 mg de recubrimiento con EC fue casi la misma. La liberación de los comprimidos con un aumento de peso de 32 mg fue más lenta que la de los comprimidos con 30 mg de aumento de peso en las primeras 5 horas de disolución. Después de 6 horas, la liberación de los comprimidos con un aumento de peso de 32 mg fue ligeramente más rápida que 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 %).

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 porcentaje de los sólidos en la solución se presentan en la Tabla 28.

Los parámetros 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 flujo de suministro de aire: 200 CFW.

Llevó 41 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 29 los pesos de los comprimidos a los 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso.

La Figura 23 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 pulverizaron un recubrimiento de Ethocel seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 30.

Los parámetros son 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 flujo de suministro de aire: 200 CFW.

Llevó 4 horas y 30 minutos agregar 30 mg de aumento de peso de la solución de recubrimiento de EC 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 peso y se registraron en la Tabla 31.

La Figura 24 muestra el % disuelto de cada una de las muestras con diferentes aumentos de peso por el recubrimiento de EC (22 mg, 24 mg, 28 mg y 30 mg de aumento de peso). A partir de la gráfica, resultó evidente que la liberación de los comprimidos con un aumento de peso de 30 mg de recubrimiento de EC fue más lenta que la los otros aumentos de peso. Cuando se compararon las velocidades de liberación de los comprimidos con aumentos de peso de 30 mg y 28 mg, sólo se observó una pequeña diferencia en la liberación. El factor de similitud f2 confirmó la similitud de las dos liberaciones (92,34 %).

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 porcentaje de los sólidos en la solución se presentan en la Tabla 32.

Los parámetros 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 flujo de suministro 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 33 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 25) muestra que los comprimidos con un aumento de peso de 7 mg de

recubrimiento final fueron los de liberación más lenta en comparación con los de 5 mg y 6 mg de aumento de peso.

Estudio sobre el lote BUP-HBr-XL-348 mg-023-5

Usando los comprimidos de 348 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 34.

Los parámetros son 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 flujo de suministro de aire: 200 CFW.

Llevó 2 horas y 16 minutos agregar 32 mg de aumento de peso de la solución de recubrimiento de EC 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 35.

El perfil de disolución (Figura 26) muestra que los comprimidos con un aumento de peso de 32 mg de recubrimiento de EC cuando se los comparó con los comprimidos con un aumento de peso de 26 mg, 28 mg, y 30 mg de recubrimiento de EC fueron los de liberación más lenta.

Estudio sobre el lote BUP-HBr-XL-348 mg-025-5

Usando los comprimidos de 348 mg, se pulverizaron un recubrimiento de Ethocel seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 36.

Los parámetros son 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 flujo de suministro de aire: 200 CFW.

Llevó 2 horas y 13 minutos agregar 32 mg de aumento de peso de la solución de recubrimiento de EC 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 37.

El perfil de disolución (Figura 27) muestra que los comprimidos con un aumento de peso de 32 mg de recubrimiento de EC cuando se los comparó con los de un aumento de peso de 26 mg fueron los de liberación más lenta al comienzo y más rápida a las 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 EC, la liberación de los comprimidos con un aumento de peso de 32 mg fue más lenta hasta las 10 horas. El factor de similitud f2 mostró que la liberación de los comprimidos con aumentos de peso de 30 mg y 32 mg fue de hecho similar (93,72 %).

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 porcentaje de los sólidos en la solución se presentan en la Tabla 38.

Los parámetros 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 flujo de suministro de aire: 200 CFW.

Se alteró la solución de recubrimiento para este lote cambiando el porcentaje de sólidos de cada componente sólido de la solución. El porcentaje de contribución de sólidos de Eudragit se redujo de 65 % a 56,5 %. El porcentaje de Syloid, Carbowax 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 a los comprimidos. Se determinaron y se registraron (Tabla 39) 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 28) muestra que los comprimidos con un aumento de peso de 7 mg fueron los de liberación más lenta de las tres muestras probadas. Sin embargo, el cálculo de f2 mostró que la liberación de los comprimidos con un aumento de peso de 6 mg fue similar a la de los de un aumento de peso de 7 mg de recubrimiento final (93,33 %).

Estudio sobre el lote BUP-HBr-XL-348 mg-026-5

Usando los comprimidos de 348 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 40.

Los parámetros son 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 flujo de suministro de aire: 200 CFW.

Llevó 2 horas y 11 minutos agregar 32 mg de aumento de peso de la solución de recubrimiento de EC 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 41.

El perfil de disolución (Figura 29) muestra que los comprimidos con un aumento de peso de 32 mg de recubrimiento de EC fueron los de liberación más lenta en comparación con las otras tres muestras con menores aumentos de peso de recubrimiento de EC (26 mg, 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 pulverizaron un recubrimiento de Ethocel seguido de un recubrimiento final sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 42.

Los parámetros son 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 flujo de suministro de aire: 200 CFW.

Llevó 3 horas y 29 minutos agregar 32 mg de aumento de peso de la solución de recubrimiento de EC a los comprimidos. Se determinaron los pesos de los comprimidos a los 22 mg, 24 mg y 26 mg de aumento de peso y se registraron en la Tabla 43.

El perfil de disolución (Figura 30) muestra que los comprimidos con un aumento de peso de 26 mg de recubrimiento de EC fueron los de liberación más lenta de las tres muestras probadas.

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 porcentaje de los sólidos en la solución se presentan en la Tabla 44.

Los parámetros 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 flujo de suministro de aire: 200 CFW.

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 45 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 31) muestra que los comprimidos con un aumento de peso de 7 mg de recubrimiento final fueron los de liberación más lenta al comienzo en comparación con los de 4 mg, 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 6: COMPRIMIDOS DE BUPROPION HBr DE ABSORCIÓN MEJORADA (EA)

Este ejemplo describe el desarrollo de comprimidos de bupropion EA "absorción mejorada" (150 mg y 300 mg). Los procedimiento de granulación, formación de comprimidos y recubrimiento se describen detalladamente en este ejemplo. Se realizaron pruebas in vitro sobre los núcleos recubiertos con EC para determinar qué formulación daba los resultados deseados.

En este estudio se usó bupropion HBr y la única diferencia con bupropion HCl es el anión. Una de las principales ventajas de la composición de absorción mejorada puede ser la disminución de la cantidad de medicamento en la composición que a su vez puede llevar a una reducción de los efectos colaterales.

En la Figura 32 se muestra un resumen del proceso global de desarrollo de los comprimidos de bupropion HBr EA.

Bupropion HBr EA - Proceso de granulación

En la Figura 33 se muestra un resumen del proceso de granulación de los comprimidos de bupropion HBr EA.

Se usaron los siguientes materiales en la granulación de los núcleos de liberación inmediata de los comprimidos de bupropion HBr EA: bupropion HBr, alcohol polivinílico y agua purificada. Una vez granulado, se agregó lubricante (Compritol 888) para completar la formulación. Se debe notar que el procedimiento de granulación para el bupropion HBr XL y el bupropion HBr EA es el mismo.

Cada ensayo se dividió en 5 partes. El porcentaje de IFA en cada formulación fue de 93,75 % y el porcentaje de PVA en cada formulación fue de 3,125 %. En la Tabla 46 se describe un resumen del desglose de cada ensayo por partes.

El alcohol polivinílico se disolvió en agua purificada usando un agitador magnético y se preparó una solución transparente e incolora.

Para granular el bupropion HBr se usó el lecho fluido NIRO con la solución de PVA en un proceso conocido como amasado húmedo.

El bupropion HBr se cargó en el lecho fluido y se inició la granulación. Las especificaciones usadas como pautas se muestran en la Tabla 47.

Se determinó la pérdida por secado después de cada granulación con el analizador de humedad. Se tomó una muestra de 1 g y se cargó en el analizador de humedad. La muestra se analizó durante 5 minutos a una temperatura de 105°C.

Después de completar la granulación de cada parte del lote, se combinaron las cinco partes. Se tamizaron a mano con un tamiz de malla n° 14 (1,4 mm) y todos los granos más grandes se pasaron a través del Comil equipado con un tamiz de 2 mm.

Se usó Compritol 888 como lubricante en la formulación. Los gránulos de bupropion HBr tamizados y el Compritol 888 se cargaron en el mezclador en V y se mezclaron durante 5 minutos. El Compritol 888 constituyó 3,125 % de la formulación. El tamaño del lote final de gránulos se describe en la Tabla 48.

Bupropion HBr EA - Proceso de formación de comprimidos

Para preparar los comprimidos de bupropion HBr se usó la compresora Beta. Según la dosis del comprimido, 150 mg o 300 mg, se usaron diferentes juegos de punzones. Se usaron los punzones de 7 mm para comprimir los comprimidos de 150 mg y los punzones de 9 mm para comprimir los comprimidos de 300 mg. Los punzones se pulieron antes de cada ciclo.

Se determinó que los pesos de los comprimidos eran 160,0 mg para los comprimidos de 150 mg de dosis y 320,0 mg para los comprimidos de 300 mg de dosis. Se hicieron estos ajustes en el peso del comprimido para compensar el hecho de que se estaba usando bupropion HBr en lugar de bupropion HCl. Las investigaciones previas mostraron que los comprimidos de bupropion HBr con los pesos antes

establecidos dieron resultados in vitro similares a los de los comprimidos de bupropion HCl de 150 mg y 300 mg. Los pesos de los comprimidos individuales tuvieron un límite de control de ± 5 %, y el peso promedio de los comprimidos tuvo un límite de control de ± 3 % (usando diez comprimidos).

Se usó un durómetro para determinar la fuerza necesaria para romper diametralmente los comprimidos (fuerza de rotura por compresión) en dos mitades iguales. Un intervalo predeterminado, entre 6,0 y 12,0 SC, estableció las especificaciones de dureza para los comprimidos de 174 mg y 348 mg.

La friabilidad se determinó usando comprimidos que tenían en total un peso de 6,5 g en un friabilómetro durante 4 minutos a 25 rpm. Los comprimidos se desempolvaron antes y después de la prueba. Se usó como criterio una pérdida de peso menor que 0,8 % a fin de aceptar o rechazar el lote.

La Tabla 49 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 50 resume las especificaciones que se mantuvieron constantes durante la compresión de todos los lotes.

Bupropion HBr EA - Proceso de recubrimiento

En la Figura 35 se muestra un resumen del proceso de recubrimiento de los comprimidos de bupropion HBr EA de 150 y 300 mg con un recubrimiento de Ethocel.

Para el recubrimiento de Ethocel de los comprimidos de bupropion HBr EA, se usó el sistema O'Hara Labcoat II de 15 pulgadas. También se usaron una boquilla de pulverización y un mezclador de hélice.

Se desarrollaron varias soluciones de recubrimiento de Ethocel que se usaron para recubrir los comprimidos de bupropion HBr. Se colocó una capa de recubrimiento de

Ethocel sobre los comprimidos que contenían una de las formulaciones que aparecen en la Tabla 51.

En la formulación 1, se pesó alcohol etílico de 200 de graduación alcohólica en un recipiente de acero inoxidable. Mientras se agitaba se agregó PEG 4000 y se permitió que se disolviera. Una vez disuelto, se agregó el Ethocel y se dejó en agitación durante 30 minutos. Después, se agregó povidona a la solución y se mezcló durante toda la noche (15 a 20 horas).

En la formulación 2, se colocó PEG 4000 en un vaso de laboratorio con sebacato de dibutilo y se agitó hasta que se disolvieron. Esto se agregó al alcohol etílico de 200 de graduación alcohólica que ya se había pesado en un recipiente de acero inoxidable. A continuación, se agregó el Ethocel y se dejó en agitación durante 30 minutos. Después, se agregó povidona y se dejó en agitación durante toda la noche (15 a 20 horas).

En la formulación 3, se colocó alcohol etílico de 200 de graduación alcohólica en un recipiente de acero inoxidable. Mientras se agitaba se agregó sebacato de dibutilo y se permitió que se disolviera. Una vez disuelto, se agregó el Ethocel y se dejó en agitación durante 30 minutos. Después, se agregó povidona a la solución y se mezcló durante toda la noche (15 a 20 horas).

En la formulación 4, se pesó alcohol etílico 95 % USP en un recipiente de acero inoxidable. Mientras se agitaba se agregó PEG 4000 y se permitió que se disolviera. Una vez disuelto, se agregó el Ethocel y se dejó en agitación durante 30 minutos. Después, se agregó povidona a la solución y se mezcló durante toda la noche (15 a 20 horas).

La Tabla 52 resume las especificaciones que se controlaron durante el proceso de recubrimiento y sus intervalos.

Estudios in vitro sobre los núcleos de bupropion HBr

Se realizó la prueba de disolución a los núcleos de bupropion HBr y a los diferentes aumentos de peso de los

núcleos recubiertos con Ethocel. Para realizar estos estudios se usó el método USP-1. La prueba de disolución se realizó usando 900 mL de HCl 0,1 N y a una velocidad de 75 rpm. Las muestras se tomaron cada hora durante 16 horas. Los perfiles de disolución se obtuvieron graficando el porcentaje acumulado de IFA disuelto en función de los tiempos de muestreo. Se mantuvieron las condiciones de sedimentación durante todos los experimentos.

En varios ensayos se utilizó el método USP-3 para realizar los estudios de disolución. Estas pruebas de disolución se realizaron durante 16 horas en total con el siguiente desglose: 2 horas usando 900 mL de líquido gástrico simulado (LGS) de pH 1,2 con 0,5 % de lauril sulfato de sodio (LSS), seguido de 2 horas en 900 mL de solución amortiguadora de acetato de pH 4,5, seguido de 12 horas en 900 mL de líquido intestinal simulado (LIS) solución amortiguadora de fosfato de pH 6,8. Estos resultados se graficaron con los datos in vivo y los datos de bupropion HCl a fin de realizar una comparación.

Estudio sobre el lote BUP-HBr-XL-016-5

La formulación se granuló usando un equipo de lecho fluido NIRO. La mezcla final se comprimió para formar comprimidos de 300 mg usando la compresora Beta con punzones cóncavos, redondos de 9 mm y para formar comprimidos de 150 mg con punzones cóncavos de 7 mm. La Tabla 53 describe la cantidad de cada material en la granulación de los comprimidos de 300 mg y la tabla 54 describe la cantidad para los comprimidos de 150 mg. Se observó que eran iguales; la única variación fue el peso del comprimido, que se ajustó en la etapa de compresión. Se hizo un primer ciclo de compresión para producir comprimidos con diferentes valores de dureza a fin de determinar los efectos de la dureza, si los hubiera, sobre la disolución (Figura 36). Se realizó una prueba de disolución a los núcleos de 300 mg y 150 mg para determinar su liberación (Figuras 37 y 38, respectivamente). Después de terminar la granulación, el lote se tamizó y antes de comprimir se agregó el lubricante (Compritol 888).

Los resultados de la granulación muestran que el tiempo de granulación promedio es de 2,0 horas y la LOD (pérdida por secado) promedio en % es de 0,342 %. Las Tablas 55 y 56 resumen los valores teóricos y reales de los parámetros que se controlaron en el proceso de compresión usando los punzones de 9 mm y 7 mm, respectivamente.

La Figura 36 muestra que los diferentes intervalos de dureza no afectaron drásticamente los perfiles de disolución. Los perfiles de disolución de los núcleos de 300 mg (Figura 37) y de 150 mg (Figura 38) muestran que los núcleos liberaban aproximadamente el 100 por ciento del IFA en una hora.

Estudio sobre el lote BUP-HBr-EA-300 mg-001-5

Usando los núcleos de los comprimidos de bupropion HBr de 300 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 57.

Los parámetros son los siguientes: velocidad de pulverización: 14 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50° C; temperatura del producto: 35° C ± 2° C; y flujo de suministro de aire: 200 CFW.

Llevó 4 horas y 4 minutos recubrir los comprimidos con un aumento de peso de 54 mg. Se determinaron y se registraron en la Tabla 58 los pesos de los comprimidos a los 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso.

El perfil de disolución (Figura 39) muestra que los comprimidos con un aumento de peso de 44 mg fueron los de liberación más rápida y los comprimidos con un aumento de peso de 54 mg fueron los de liberación más lenta de los 6 aumentos de peso diferentes que se probaron.

En este ensayo también se realizó la disolución mediante USP3, sobre el comprimido de 52 mg de aumento de peso. El

perfil de disolución se graficó como tiempo en horas contra % disuelto y se graficó junto con los datos in vivo y los datos de bupropion HCl a fin de realizar una comparación. Los resultados (Figura 40) mostraron que el ensayo no coincidía con los datos in vivo, ni coincidía con los datos de bupropion HCl.

Estudio sobre el lote BUP-HBr-EA-150 mg-002-5

Usando los comprimidos de 150 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 59.

Los parámetros son los siguientes: velocidad de pulverización: 14 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50° C; temperatura del producto: 35° C ± 2° C; y flujo de suministro de aire: 200 CFW.

El proceso de recubrimiento de este ensayo demoró 4 horas y 38 minutos en lograr un aumento de peso de 36 mg. Se determinaron y se registraron en la Tabla 60 los pesos de los comprimidos a los 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg y 36 mg de aumento de peso.

El perfil de disolución (Figura 41) muestra que los comprimidos con un aumento de peso de 18 mg y 20 mg de recubrimiento de EC fueron los de liberación más rápida de todo los aumentos de peso probados. Fue evidente que la liberación de los comprimidos con un aumento de peso de 36 mg fue la más lenta en comparación con la de todos los otros aumentos de peso.

Estudio sobre el lote BUP-HBr-EA-300 mg-003-5

Usando los comprimidos de 300 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 61.

Los parámetros son los siguientes: velocidad de pulverización: 14 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50° C; temperatura del producto: 35° C ± 2° C; y flujo de suministro de aire: 200 CFW.

Llevó 4 horas y 13 minutos agregar 54 mg de aumento de peso de la solución de recubrimiento de EC a los comprimidos. Se determinaron los pesos de los comprimidos a los 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso y se registraron en la Tabla 62.

El perfil de disolución (Figura 42) muestra que los comprimidos con un aumento de peso de 52 mg de recubrimiento de EC fueron los de liberación más lenta cuando se los comparó con los otros perfiles con diferentes aumentos de peso.

Estudio sobre el lote BUP-HBr-EA-300 mg-004-5

Usando los comprimidos de 300 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 63.

Los parámetros son los siguientes: velocidad de pulverización: 14 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50° C; temperatura del producto: 35° C ± 2° C; y flujo de suministro de aire: 200 CFW.

Llevó 4 horas y 13 minutos agregar 54 mg de aumento de peso de la solución de recubrimiento de EC a los comprimidos. Se determinaron los pesos de los comprimidos a los 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso y se registraron en la Tabla 64.

El perfil de disolución (Figura 43) muestra que los comprimidos con un aumento de peso de 52 mg fueron los de liberación más lenta cuando se los comparó con los otros

perfiles y los comprimidos con un aumento de peso de 44 mg de recubrimiento de EC fueron los de liberación más rápida.

Estudio sobre el lote BUP-HBr-EA-300 mg-005-5

Usando los comprimidos de 300 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 65.

Los parámetros son los siguientes: velocidad de pulverización: 14 g/min; velocidad de la paila: 12,0 rpm; aire de entrada: 50° C; temperatura del producto: 35° C ± 2° C; y flujo de suministro de aire: 200 CFW.

Llevó 4 horas y 14 minutos agregar 54 mg de aumento de peso de la solución de recubrimiento de EC a los comprimidos. Se determinaron los pesos de los comprimidos a los 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso y se registraron en la Tabla 66.

La Figura 44 muestra que los comprimidos con un aumento de peso de 54 mg fueron los de liberación más lenta cuando se los comparó con los otros perfiles y que los comprimidos con un aumento de peso de 44 mg de recubrimiento de EC fueron los de liberación más rápida de los seis perfiles.

Estudio sobre el lote BUP-HBr-EA-150 mg-006-5

Usando los comprimidos de 150 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 67.

Los parámetros son los siguientes: velocidad de pulverización: 14 g/min; velocidad de la paila: 12,0 rpm;

aire de entrada: 50° C; temperatura del producto: 35° C ± 2° C; y flujo de suministro de aire: 200 CFW.

El proceso de recubrimiento de este ensayo demoró 4 horas y 36 minutos en lograr un aumento de peso de 36 mg. Se determinaron y se registraron en la Tabla 68 los pesos de los comprimidos a los 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg y 36 mg de aumento de peso.

El perfil de disolución (Figura 45) muestra que los comprimidos con un aumento de peso de 36 mg de recubrimiento de EC fueron los de liberación más lenta cuando se los comparó con los otros cuatro perfiles (24 mg, 28 mg, 32 mg y 34 mg de aumento de peso).

También se llevó a cabo la prueba de disolución USP-3 en este ensayo, para ver si los resultados se parecían a los datos in vivo y a los datos in vitro del bupropion HCl 300 mg de referencia. El perfil de disolución (Figura 46) muestra que los comprimidos de bupropion HBr EA de 150 mg con un aumento de peso de 24 mg fue similar al perfil in vivo.

Estudio sobre el lote BUP-HBr-EA-150 mg-007-5

Usando los comprimidos de 150 mg, se pulverizó un recubrimiento de Ethocel sobre los comprimidos, con el equipo de recubrimiento O'Hara Labcoat II.

Los materiales usados en el recubrimiento de Ethocel (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 69.

EJEMPLO 7: ESTUDIOS COMPARATIVOS DE DEGRADACIÓN FORZADA SOBRE PRODUCTOS FARMACÉUTICOS DE BUPROPION HCl Y BUPROPION HBr

Se colocaron los comprimidos de bupropion HCl y HBr (recubiertos con EC y recubiertos con EC más una barrera contra la humedad) individualmente en un vidrio de reloj sin tapar, y se expusieron a condiciones aceleradas de 40° C/75 % de HR en la cámara de estabilidad. Después de 13 y 20 días, se midió el contenido de las muestras y se realizó el análisis de impurezas de acuerdo con el método de HPLC P05.901.10.

La Tabla 70 y la Figura 47 muestran los resultados de 13 y 20 días del estudio de degradación forzada en los comprimidos de bupropion HCl y HBr recubiertos con EC. Para el producto de bupropion HCl, las impurezas de degradación principales 3-CBZ y 852U77 fueron 0,12 % y 0,38 % respectivamente, mientras que para el bupropion HBr, estos valores fueron 0,07 % y 0,49 %, respectivamente. Las demás impurezas de degradación y las totales desconocidas fueron muy similares para los dos productos; sin embargo, el valor del contenido para el producto de HBr fue mayor que para el de HCl. La diferencia en el contenido y en el nivel de impurezas resultó más importante en los productos farmacéuticos finales. Como se muestra en la Tabla 71 y en la Figura 48, para el mismo periodo del estudio el contenido de bupropion HCl fue menor (95,5 %) y los niveles de los productos de degradación e impurezas desconocidas fueron mayores (3-CBZ: 0,28 %, 852U77: 1,23 %, 827U76: 0,10 % y totales 1,73 %) que para el bupropion HBr (3-CBZ: 0,12 %, 852U77: 0,41 %, 827U76: 0,05 % y totales 0,75 %).

EJEMPLO 8: ESTUDIOS ADICIONALES DE DEGRADACIÓN FORZADA SOBRE BUPROPION HBr Y BUPROPION HCl EN PRESENCIA DE EXCIPIENTES

Se realizaron estudios adicionales de degradación forzada a 55°C, a 55°C y 100 % de humedad relativa, a 100°C, y a 105°C en ambas sales de bupropion HCl y HBr en presencia de excipientes. El peso promedio de los excipientes y el peso del ingrediente farmacéutico activo (IFA) presentes en las muestras se muestran en la Tabla 72. Los resultados de este estudio se muestran en las Figuras 49-53. La Figura 49 muestra la cantidad de impureza 3-CBA en las diversas muestras. La Figura 50 muestra la cantidad de impureza 852U77 en las diversas muestras. La Figura 51 muestra la cantidad de impureza 20U78 en las diversas muestras. La Figura 52 muestra la cantidad de impureza 827U76 en las diversas muestras. La Figura 53 es una gráfica que muestra la pérdida de cada sal en el tiempo en un experimento de TGA a 100°C. Estos resultados indican que a temperaturas elevadas ocurre una dismutación de la sal de HCl con pérdida concomitante de HCl gaseoso. Esta dismutación no ocurrió en la sal de HBr.

Los resultados muestran claramente que el bupropion HBr presenta mejoras significativas en su estabilidad en comparación con el bupropion HCl. La degradación del bupropion HBr fue más lenta como lo indica la formación de cantidades menores de impurezas en comparación con el bupropion HCl.

EJEMPLO 9: PREPARACIÓN DE COMPRIMIDOS ADICIONALES DE BUPROPION HBr EA

Con los procedimientos descritos en el Ejemplo 6, se prepararon comprimidos adicionales de bupropion EA usando las cantidades que se muestran en la Tabla 73.

EJEMPLO 10: ESTUDIOS DE ESTABILIDAD ACELERADA DE BUPROPION HBr

La estabilidad de bupropion HBr se evaluó en las condiciones aceleradas de 40°C ± 2°C y 75 % ± 5 % de HR en una cámara de estabilidad. Las muestras se prepararon en frascos cerrados y se colocaron en la cámara de estabilidad. Se realizó el análisis por HPLC de las muestras antes de colocarlas en la cámara de estabilidad (tiempo 0) y después de 3 meses y 6 meses. La cantidad de los principales productos de degradación presentes a tiempo 0 se comparó con las cantidades presentes después de 3 meses y 6 meses. Como se muestra en las Tablas 74-76 se analizaron tres lotes diferentes de bupropion HBr. Para cada muestra analizada, en cada periodo de tiempo se hicieron dos análisis diferentes por HPLC. El primer análisis rotulado pureza cromatográfica A, midió el porcentaje de tres impurezas 3'-cloropropiofenona, 3'-cloro-2-bromopropiofenona y ácido 3-clorobenzoico. El segundo análisis rotulado pureza cromatográfica B, midió el porcentaje de 2-N-(tercbutil)-aminopropiofenona, una única impureza desconocida y el total de impurezas desconocidas. Finalmente se informó el porcentaje total de impurezas (conocidas y desconocidas) para cada muestra. A partir de los datos presentados se puede observar que hay un ligero aumento en la impureza 3'-cloropropiofenona. Aunque se vieron variaciones leves en el porcentaje de otras impurezas no se encontró una tendencia que mostrara un aumento de dichas impurezas en los periodos de tiempo de 3 y 6 meses en que se midieron. El porcentaje total de impurezas para cada una de las

muestras de HBr no cambió ni a los 3 meses ni a los 6 meses. Estos resultados indican que la sal de HBr de bupropion fue muy estable en las condiciones de prueba de estabilidad acelerada.

EJEMPLO 11: PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL

La estabilidad del bupropion HBr se estudió en un periodo más largo en condiciones que intentaban aproximarse a condiciones de almacenamiento y vida útil normales. Las muestras se prepararon en envases cerrados y se sometieron a almacenamiento a largo plazo a 25°C ± 2°C y 60 % ± 5 % de HR en una cámara de estabilidad. Las muestras se analizaron por HPLC antes de colocarlas en la cámara de estabilidad (tiempo 0) y después de 3 meses y 6 meses. La cantidad de los productos de degradación principales presentes a tiempo 0 se comparó con las cantidades presentes después de 3 meses y 6 meses. Como se muestra en las Tablas 77-79 se analizaron tres lotes diferentes de bupropion HBr. Como en el Ejemplo 10 cada muestra se analizó en dos condiciones de análisis por HPLC para identificar 6 impurezas o grupos de impurezas como se describió en el Ejemplo 10. A partir de los resultados que se muestran en las tablas 77-79 se puede ver que el porcentaje de la impureza 3'-cloropropiofenona aumentó ligeramente con el tiempo. Aunque las demás impurezas variaron ligeramente no presentaron una tendencia a aumentar con el tiempo. Estos resultados demuestran la estabilidad de bupropion HBr en condiciones de almacenamiento normales durante un periodo de tiempo largo.

EJEMPLO 12: ESTUDIO DE PREPARACIÓN Y ESTABILIDAD DE FORMAS POLIMÓRFICAS I, II Y III DE BUPROPION HBr.

Las formas polimórficas I, II y III del bromhidrato de bupropion se prepararon de la siguiente manera y su estabilidad se estudió en las condiciones descritas a continuación:

Forma I:

Se cargaron 34 g de base de bupropion y 138 ml de isopropanol en un matraz de 250 ml equipado con un agitador en la parte superior y una entrada para gas. La solución se mantuvo bajo agitación mientras se introducían 13 g de HBr gaseoso a través de la entrada de

gas en un tiempo de 20 minutos mientras la temperatura interna de la mezcla aumenta de 25 a 40°C. Durante la adición del gas se formó un precipitado blanco pesado. Al final de la adición del gas la temperatura de la mezcla se elevó hasta reflujo (80°C), para lograr la disolución completa del sólido suspendido. La temperatura se redujo entonces a 25°C en 1 hora y se redujo aun más hasta 0-5°C en 1 hora adicional. El precipitado obtenido se filtró y se lavó con 20 ml de isopropanol frío. El sólido húmedo descargado se secó al vacío (30 mm Hg) en un secador estático a 50°C durante 16 horas. Se obtuvieron 34 g de forma I de bromhidrato de bupropion.

Las muestras de la forma I de bupropion HBr se sometieron a las condiciones del estudio de estabilidad acelerado que se describió en el Ejemplo 10 y al estudio de estabilidad de vida útil que se describió en el Ejemplo 11. Los estudios de PXRD realizados después de 3 meses y 6 meses para cada una de las muestras dieron los mismos resultados. El perfil de PXRD de una de las muestras después de 6 meses en las condiciones de estabilidad aceleradas se muestra en la Figura 60.

Forma II:

Se disolvieron 10 g de la forma I de bupropion HBr en una mezcla de 170 ml de acetona y 7 ml de agua. La mezcla se puso a reflujo con disolución del sólido. La solución se enfrió después hasta temperatura ambiente. Después de una noche el precipitado formado se filtró y se secó a 40°C al vacío (30 mm Hg) durante 12 horas. Se obtuvieron 2,4 g de la forma II de bupropion HBr. Una muestra del producto se preparó para la prueba de estabilidad acelerada, en condiciones de la ICH (conferencia internacional sobre armonización de requisitos técnicos para el registro de fármacos para uso humano), (40°C/75 % de H.R.), sellando el producto en bolsas de polietileno, que a su vez se colocaron en bolsas de aluminio que contenían sílice y se sellaron y colocaron en la cámara de estabilidad en condiciones de la ICH (40°C/75 % de H.R.). La forma cristalina se verificó después de mantener el producto en estas condiciones durante 1 mes. El perfil de PXRD que aparece en la Figura 61 muestra que el compuesto aún está en la forma II. Esto demuestra la estabilidad de la forma cristalina II en estas condiciones.

Forma III:

Se colocaron 20 g de la forma I de bromhidrato de bupropion y 96 ml de etanol absoluto en un matraz de 250 ml. La mezcla se puso a reflujo obteniéndose la disolución completa del sólido. La solución se enfrió después hasta temperatura ambiente sin agitación y se dejó en estas condiciones durante 18 horas. El sólido cristalino resultante se filtró a continuación y se secó al vacío (30 mm Hg) a 50°C durante 4 horas. Se obtuvieron 11,2 g de la forma III de bupropion HBr. Se preparó una muestra del producto para la prueba de estabilidad sellando el producto en bolsas de polietileno que a su vez se colocaron en bolsas de aluminio que contenían sílice y se sellaron, y se colocaron en la cámara de estabilidad en condiciones de la ICH (40°C/75 % de HR.). La forma cristalina se verificó después de mantener el producto en estas condiciones durante 1 mes. El perfil de PXRD que se muestra en la Figura 62 demuestra que el producto no es estable en esta forma en estas condiciones, ya que la mayoría del producto cambió a la forma II.

EJEMPLO 13: Comprimidos HBr-SR para dosis de 100 y 150 mg como alternativa a HCl-SR

Formulación que se basará en las opciones usadas durante el desarrollo del Wellbutrin HCl SR 100 y 150 mg.

El bupropion HCl se reemplazó con HBr y se ajustó para obtener la misma cantidad de bupropion base.

Los materiales de relleno se ajustaron de forma acorde para obtener los mismos pesos de los núcleos de los comprimidos,

ej. 150 mg HCl = 130 mg base = 174 mg HBr
100 mg = 86,7 = 116

Proceso de granulación de HBr:

El bupropion HBr se granula con una solución acuosa que contiene alcohol polivinílico y un estabilizante como ácido oxálico o ácido succínico o ácido aspártico u otro compuesto ácido adecuado, en un granulador de lecho fluido.

Los gránulos secos se mezclan después con un polímero soluble en agua o una mezcla de polímeros hidrófobos/hidrófilos con varios grados de viscosidad. En los ensayos se usaron Hipromelosa (hidroxipropil metilcelulosa K4M grado CR) así como hidroxipropil celulosa (HPC) en cantidades suficientes para obtener la liberación deseada.

Se usó celulosa microcristalina (CMC) como relleno y como material aglutinante. Se puede reemplazar con lactosa. Para la lubricación final se usó behenato de glicerilo (Compritol 888 ATO). Otros lubricantes como ácido esteárico y fumarato de sodio son adecuados.

Los comprimidos se recubren después con una solución de película de recubrimiento coloreada no funcional.

Ejemplo de formulación: mg/unidad (peso deseado 400 mg) para dosis de 174 mg (equivalente a 150 mg HCl).

Bupropion HBr	174 mg
Alcohol polivinílico	16
Estabilizador	20
HPMC (HPC)	40
CMC	144
Behenato de glicerilo	6

Recubrimiento: Opadry suministrado por Colorcon, aproximadamente 3-4 % de aumento de peso.

Las formulaciones anteriores se evaluan sin usar estabilizadores.

EJEMPLO 14: ESTUDIOS DE ESTABILIDAD ADICIONALES:

Estabilidad de bupropion HBr en comprimidos de 348 mg

En estos estudios, se probó la estabilidad de comprimidos de bupropion HBr (Lote núm. Bup-HBr-XL-348-025-5 (7, 30 y 90 unidades)) después de almacenar a 40 grados C y 75 % de humedad relativa como ya se describió para los comprimidos de 348 mg preparados según se describió antes y que tienen la composición del comprimido que se muestra en la Tabla 99. Estos experimentos evaluaron los resultados de la estabilidad acelerada de los comprimidos de bupropion HBr XL de 348 mg envasados como 7, 30 y 90

unidades basados en la comparación de los cambios en el aspecto físico, el contenido, el nivel de impurezas de degradación conocidas y los perfiles de disolución a los 1, 2, 3 y 6 M con los datos iniciales.

No se observaron cambios significativos en el aspecto físico y los valores de contenido de los comprimidos para todas las presentaciones, sin embargo, como se esperaba, hubo un aumento gradual en los niveles de las dos principales impurezas de degradación conocidas (3-CBZ y 852U77) y al pasar 7 a 90 unidades, los porcentajes de las dos últimas fueron variados. Los perfiles de disolución del producto farmacéutico para todas las presentaciones fueron menores en el primer mes para todos los tiempos de muestreo en comparación con el perfil inicial, sin embargo, los demás tiempos de muestreo de la estabilidad variaron, por ejemplo:

7 unidades: los de 2 M y 3 M fueron similares al del inicio y los de 6 M similar a los de 1 M.

30 unidades: El de 6 M fue similar al de 1 M y menor que el inicial, los tiempos de muestreo de 2 y 4 horas para 2M y 3M fueron similares al inicial, sin embargo, los tiempos de muestreo de 8 y 16 horas fueron menores que los valores correspondientes.

90 unidades: Esencialmente se observaron perfiles de disolución menores para 2M, 3M y 6M en comparación con los perfiles iniciales. Estos resultados aparecen en la Figura 63.

EJEMPLO 15: PRUEBAS DE ESTABILIDAD ADICIONAL DE COMPRIMIDOS DE BUPROPION HBr DE 150 mg Y 300 mg (Lotes núm. Bup-Hbr-Ea-150-002-5 y Bup-Hbr-300-001-5)

Se usaron los mismos criterios para evaluar la estabilidad de los productos farmacéuticos de bupropion HBr EA 150 y 300 mg para las 90 unidades. Se obtuvieron resultados similares para los dos productos farmacéuticos en comparación con los comprimidos de bupropion HBr XL 348 XL 348 mg, 90 unidades, sin embargo, se observaron mejores datos de estabilidad de disolución, es decir, no se observaron diferencias significativas en los perfiles de disolución para 1M, 2M, 3M y 6M para los dos productos

EA en comparación con sus valores iniciales correspondientes, excepto los datos de disolución a 6M para los 300 mg que mostraron valores ligeramente menores. Estos resultados están en la Figura 64.

EJEMPLO 16: Estudios adicionales de estabilidad en vidrio de reloj sin tapar y frasco cerrado

Se realizaron experimentos para comparar la estabilidad de núcleos de bupropion HBr XL 174 mg, núcleos de bupropion HBr XL 348, núcleos de bupropion HCl XL 150 mg y núcleos de bupropion HCl XL 300 mg durante 10 y 20 días en condiciones de frasco abierto y frasco cerrado. Estos estudios se efectuaron nuevamente a 40 grados C y 75 % de humedad relativa. La degradación se evaluó nuevamente mediante el análisis de las impurezas conocidas 3-CBZ y 852U77. Igual que antes, los núcleos de bupropion HBr se degradaron menos que los núcleos de bupropion HCl en condiciones de frasco abierto y frasco cerrado. Estos resultados se presentan en la Figura 65.

EJEMPLO 17: DISOLUCIÓN DE FORMULACIONES DE BUPROPION DE ACUERDO CON LA INVENCIÓN EN DIFERENTES MEDIOS DE USP-3

Se evaluó la disolución de formulaciones de bupropion HBr de acuerdo con la invención en tres medios USP-3, es decir, LGS de pH 1,2, solución amortiguadora de acetato de pH 4,5 y solución amortiguadora de fosfato de pH 6,8 en un periodo de 16 horas. Estos resultados se presentan en la Figura 66. En particular los comprimidos (finales) de Bupropion HBr XL de 348 mg Lote núm. Bup-HBr-XL-012-5, los comprimidos (finales) de 300 mg de Wellbutrin XL Lote núm. 05A116, los comprimidos de Bupropion HBr XL de 348 mg (EC1) Lote N° Bup-HBr-XL-012-5 (EC 32 mg de peso) y los comprimidos de Wellbutrin XL de 300 mg (EC10) Lote núm. 05D047 se evaluaron en medio LGS de pH 1,2 durante 2 horas, solución amortiguadora de acetato de pH 4,5 durante 2 horas y solución amortiguadora de fosfato LIS de pH 6,8 durante un total de 10 horas. Estos resultados se presentan en la Figura 66-68.

Además, la Figura 66 contiene los resultados de las pruebas de disolución de una formulación de bupropion HBr de acuerdo con la invención, es decir, bupropion HBr 348 mg, lote núm. 05E304, contra BupHCl 300 mg (Bup 300XL de referencia) lote núm. 01L238 in vivo y BUP 300XL de

referencia en medio LSS USP-3 al 0,5 % en tiempos entre 0 y 16 horas.

Además la misma figura presenta la tabla de resultados de estos experimentos de disolución que comparan el porcentaje de liberación de fármaco en el tiempo para bupropion HBr 348 mg lote núm. 05E304 en medio USP-3 (LGS pH 1,2 y LSS 0,5 % después de 2 horas, solución amortiguadora de acetato a pH 4,5 después de 2 horas y solución amortiguadora de fosfato a pH 6,8 después de 16 horas en total.

También, la Figura 68 contiene perfiles de disolución comparativos para comprimidos de bupropion HBr XL de 348 mg final y Wellbutrin XL EC en diferentes medios USP-3 (LGS de pH 1,2, solución amortiguadora de acetato de pH 4,5 y solución amortiguadora de fosfato de pH 6,8) comparados contra los datos in vivo para bupropion HCl 150 mg XL de referencia (lote 02A063) en un periodo de 16 horas.

Tabla 1

Determinación de contenido de las sales de bupropion por HPLC

Pruebas:	Maleato	Tosilato	Fumarato	HBr	Succinato	Tartrato ácido	Tartrato neutro	Citrato
Contenido	99,7 %	97,4 %	89,8 %	99,7 %	97,6	84,9 %	51,7 %*	85,0 %

Tabla 2

Contenido de humedad y pH de las soluciones acuosas:

ID de la muestra	Original (IFA iniciales)		Después de recristalizar (R y D)		
			Analizada después de 1 día		Analizada después de 2 meses
	KF	pH (ac. 0,5 %)	KF	pH (ac. 0,5 %)	KF
Bup-HCl	0,0	5,90			
Bup-Maleato	0,10	4,29			
Bup-Tosilato	1,71*	5,56	023	5,88	0,18
Bup-Fumarato	0,09	3,84			
Bup-HBr	0,00	5,92			
Bup-Succinato	0,13	4,82			
Bup-Tartrato	0,18	3,62			
Bup-Tartrato neutro	0,14	3,62			
Bup-Citrato (I)	0,23	3,89			

*KF después de 3M = 1,80 %

Bup = bupropion

Tabla 3

Solubilidad y otras propiedades físicas: bupropion HBr frente a bupropion HCl.

ID de la muestra	Solubilidad (mg/ml)		
	Agua	EtOH	AIP
Bupropion HCl	270	80	10
Bupropion HBr	143	92	12

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ID de la muestra	PS (Malvern)	Contenido de humedad (KF)	pH (ac. 0,5 %)	PF (SFC)
Bupropion HCl (Erregierre)	10 % 32 µm 50 % 102 µm 90 % 276 µm	0,01 %	5,90	243,6°C
Bupropion HBr (Chemi)	10 % 72 µm 50 % 245 µm 90 % 657 µm	0,00 %	5,92	234,1°C

Tabla 4

40°C/75 % de HR			
Vial cerrado			
(SF + Placebo)[1]	(SF + Placebo)[1] + agua[2]	(SF + Placebo)[1] + (agua + EtOH + AIP)[3]	(SF + Placebo)[1] + (AIP + EtOH)[4]

[1] 300 mg de la sustancia farmacéutica se colocaron en un vial de 2 mL, se agregaron 100 mg de placebo (casi el doble de la cantidad necesaria) y se mezclaron bien.

[2] Se agregaron dos gotas de agua al placebo con agregado de cantidad conocida y se mezclaron bien con una espátula, después se cerró con una copa.

[3] Se preparó una mezcla con volúmenes iguales de agua, EtOH y AIP. Se agregaron dos gotas de dicha mezcla al placebo con agregado de cantidad conocida y se mezclaron bien con una espátula, después se cerró con una copa.

[4] Se preparó una mezcla con volúmenes iguales de EtOH y AIP. Se agregaron dos gotas de dicha mezcla al placebo con agregado de cantidad conocida y se mezclaron bien con una espátula, después se cerró con una copa.

Tabla 5

ID del IFA	N° de Lote	Cantidad/ frasco	N° de frasco de vidrio 40°C/75 % HR	Tiempo final de la estabilidad (día)
Bupropion HBr	STN07492	348 mg	2	14 y 24
Bupropion HCl	STN06973	300 mg	2	14 y 24
Bupropion HBr	STN07491	348 mg	1	10
	STN07492	348 mg	1	10
Bupropion HCl	STN06973	300 mg	1	10
	STN06978	300 mg	1	10

Tabla 6

Estudios de estabilidad en frasco de vidrio cerrado (40°C/75 % de HR) sobre los IFA bupropion HBr y HCl.

Pruebas	Inicial	Bupropion HBr, N° Lote STN07492		Inicial	Bupropion HCl, N° Lote. STN06973	
		14 días	24 días		14 días	24 días
contenido %	99,6	98,8	99,5	100,4	98,5	98,5
Impurezas %						
3-CBZ	0,007	0,015	0,022	0,002	0,019	0,082
852U77	0,009	0,058	0,052	0,003	0,010	0,023
20U78/dilu	0,044	0,048	0,038	0,043	0,038	0,040
827U76	ND	0,012	0,016	ND	ND	0,102
Desconocidas totales	0,098	0,105	0,104	0,044	0,038	0,049
Total (%)	0,16	0,23	0,23	0,09	0,11	0,30

Tabla 7

Estudios de estabilidad en frasco de vidrio cerrado (40°C/75 % de HR) sobre los IFA bupropion HCl y bupropion HBr.

Pruebas	Inicial	Bupropion HBr, N° Lote STN07491	Inicial	Bupropion HBr, N° Lote STN07492
		10 días		10 días
contenido %	99,5	98,2	99,6	99,2
Impurezas %				
3-CBZ	0,011	0,070	0,007	0,031
852U77	ND	0,125	ND	0,055
20U78/dilu	0,041	0,051	0,041	0,044
827U76	ND	0,039	ND	ND
Desconocidas totales	0,129	0,129	0,194	0,15
Total (%)	0-17	0,42	0,23	0,24
Pruebas	Inicial	Bupropion HCl, N° Lote STN06973	Inicial	Bupropion HCl, N° Lote STN06978
		10 días		10 días
contenido %	99,4	96,3	99,1	96,5
% de impurezas				
3-CBZ	0,003	0,110	0,002	0,278
852U77	ND	0,047	ND	0,124
20U78/dilu	0,040	0,047	0,04	0,057
827U76	ND	0,045	ND	0,141
Desconocidas totales	0,053	0,187	0,165	0,137
Total (%)	0,10	0,44	0,21	0,74

Tabla 9

Resumen de las especificaciones para el procedimiento de granulación.

Especificación	Intervalo	Referencia
Velocidad del ventilador	Lenta	Lenta
Volumen de aire (CMH)	60-65	65
Temperatura de salida (°C)	35-45	40
Temperatura de suministro (°C)	60-65	65
Temperatura del producto (°C)	35-55	45
Presión del aire de pulverización (Bar/psi)	35	35
Velocidad de bomba (rpm)	18	18
Velocidad de flujo del líquido (g/min)	13	13
Punto de rocío del lecho (MMWC)	0	0
Punto de rocío del filtro (MMWC)	100-300	200

Tabla 8

Contenido de cada ensayo y cantidad de cada material en cada parte

Materiales	Cantidad (g)				
	Parte 1	Parte 2	Parte 3	Parte 4	Parte 5
Bupropion HBr	2.062,5	2.062,5	2.062,5	2.062,5	2.062,5
PVA	68,75	68,75	68,75	68,75	68,75
Agua purificada	1.452,5	1.452,5	1.452,5	1.452,5	1.452,5

Tabla 10

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	2.131,25
Parte 2	2.131,25
Parte 3	2.131,25
Parte 4	2.131,25
Parte 5	2.131,25
Compritol 888	343,75
Total	11.000,0

Tabla 11

Resumen de especificaciones para el ajuste de la compresora de comprimidos.

Parámetros	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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Tabla 12

Resumen de las especificaciones para la compresión

Parámetros	Especificación para comprimido de 174 mg	Especificación para comprimido de 348 mg
Peso de cada comprimido (mg)	185,6 ± 5 %	371,2 ± 5 %
	(176,3 mg-194,9 mg)	(352,6 mg-389,8 mg)
Peso promedio de los comprimidos (mg)	185,6 ± 3 %	371,2 ± 3 %
	(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

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Tabla 13

Formulaciones usadas como el recubrimiento de Ethocel en los núcleos de bupropion HBr de 174 mg y 348 mg.

FORMULACIÓN 1	FORMULACIÓN 2	FORMULACIÓN 3
Ethocel (etilcelulosa) Estándar 100 Premium	Ethocel (etilcelulosa) Estándar 100 Premium	Ethocel (etilcelulosa) Estándar 100 Premium
Povidona USP (Kollidon 90F)	Povidona USP (Kollidon 90F)	Povidona USP (Kollidon 90F)
Polietilenglicol 4000	Polietilenglicol 4000	Polietilenglicol 4000
Alcohol etílico 95 % USP	Sebacato de dibutilo	Alcohol etílico 95 % USP
Alcohol isopropílico (AIP)	Alcohol etílico 95 % USP	

Tabla 14

Formulaciones usadas como los recubrimientos finales en los comprimidos de bupropion HBr de 174 mg y 348 mg.

FORMULACIÓN A	FORMULACIÓN B
- Eudragit L30D-55 - Chroma-Tone DEB 5156-CLE - Agua purificada	- Eudragit L30D-55 - Syloid 244FP - Polietilenglicol 4000 - Citrato de trietilo - Agua purificada

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Tabla 15

Resumen de especificaciones que se mantuvieron constantes en el proceso de recubrimiento con Ethocel.

Parámetros del proceso	Intervalos de operación	Referencia
Temperatura de entrada para recubrimiento (°C)	SV: 40 ± 5	40
	PV: 40 ± 5	
Temperatura de entrada para secado (°C)	30-35	35
Temperatura de salida	30 ± 10	30
Temperatura del producto	25-35	28
Presión diferencial ΔP (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 pulverización (psi)	35-40	35
Aire patrón (psi)	20-30	25
Velocidad de pulverización (g/min)	5-15	6,0

Tabla 16

Resumen de especificaciones que se mantuvieron constantes en el proceso de recubrimiento final.

Parámetros del proceso	Intervalos de operación	Referencia
Temperatura de entrada para recubrimiento (° C)	SV: 50 ± 5 PV: 50 ± 5	50
Temperatura de entrada para secado (° C)	40 ± 5	40
Temperatura de salida	35 ± 5	38
Temperatura del producto	35 ± 2	35
Presión diferencial ΔP (W.C)	(-0,1)-(-0,12)	-0,10
Flujo de suministro de aire (CFM)	200 ± 50	200
Velocidad de la paila (rpm)	2,5-15	12,0
Aire de pulverización (psi)	25-35	35
Aire patrón (psi)	20-30	25
Velocidad de pulverización (g/min)	5-15	13,0

Tabla 17

Materiales usados en una parte del lote, porcentaje de cada componente, cantidad por comprimido y cantidad por lote, para BUP-HBr-XL-009-5

Materiales	%	mg/comprimido	Cantidad en el lote (g)
Bupropion HBr	93,75	348,00	1.993,75
PVA	3,125	11,60	68,75
Compritol 888	3,125	11,60	68,75
Total	100,00	371,2 mg	2.131,25

Tabla 18

Resultados obtenidos usando punzones de 9 mm para el lote BUP-HBr-XL-009-5.

Parámetros	Teórico	Real
Peso promedio de los comprimidos	371,2 mg	371,5 mg
Dureza promedio	6,0-12,0 SC	10,77 SC
Espesor promedio	5,0-6,0mm	5,60 mm
Friabilidad	<0,8 %	0 %

Tabla 19

Resultados obtenidos usando punzones de 10 mm para el lote BUP-HBr-XL-009-5.

Parámetros	Teórico	Real
Peso promedio de los comprimidos	371,2 mg	366,5 mg
Dureza promedio	6,0-12,0 SC	7,50 SC
Espesor promedio	5,0-6,0 mm	4,97 mm
Friabilidad	<0,8 %	0 %

Tabla 20

Materiales usados en una parte del lote, porcentaje de cada componente, cantidad por comprimido y cantidad por lote, para el lote BUP-HBr-XL-021-5

Materiales	%	mg/comprimido	Cantidad en el lote (g)
Bupropion HBr	93,75	174,00	1.993,75
PVA	3,125	5,80	68,75
Compritol 888	3,125	5,80	68,75
Total	100,00	185,60	2.131,25

Tabla 21

Resultados obtenidos usando punzones de 7 mm para el lote BUP-HBr-XL-021-5.

Parámetros	Teórico	Real
Peso promedio de los comprimidos	185,6 mg	186,8 mg
Dureza promedio	6,0-12,0 SC	9,23 SC
Espesor promedio	4,5-5,0 mm	4,70 mm
Friabilidad	<0,8 %	0 %

5

Tabla 22

Materiales usados en el recubrimiento EC y sus cantidades para el lote BUP-HBr-XL-348-013-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución
Ethocel (etilcelulosa) estándar 100 Premium	3,60	77,44*	38,74
Povidona USP (Kollidon 90F)	4,600	99,22*	49,64
PEG 4000	1,07	23,23*	11,62
Alcohol etílico 95 % USP	86,44	1.859,50	N/A
Alcohol isopropílico 99 % USP	4,54	97,87	N/A
Total	100,00	2.151,00	100,00

*El total de componentes sólidos de la formulación incluyó 77,44 g de Ethocel, 99,22 g de povidona y 23,23 g de PEG 4000, que dieron una cantidad de sólidos totales de 199,89 g. El componente sólido de la formulación constituyó hasta el 9 % del total de la solución y el restante 91 % lo constituyó el líquido.

Tabla 23

Pesos teóricos 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 (mg)	Peso teórico (mg)	Peso real (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

Tabla 24

Materiales usados en el recubrimiento final y sus cantidades para el lote BUP-HBr-XL-348-013-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	Cantidad de sólido (g)	% de sólidos en solución
Eudragit L30 D-55	22,73	104,8	31,44	65,00*
Chroma-Tone DEB 5156-CLE	3,66	16,90	16,90	35,00**
Agua purificada (1)	21,78	100,40	N/A	N/A
Agua purificada (2)	51,89	239,20	N/A	N/A
Total	100,00	460,95	48,34***	100,00

*El porcentaje de Eudragit, sólido, que contribuyó a la cantidad total de sólidos fue de 65 %.

**El porcentaje de Chroma-Tone, sólido, que contribuyó a la cantidad total de sólidos fue de 35 %.

***La cantidad total de sólidos (48,34 g) fue de 10,5 % del total de la solución.

Tabla 25

Pesos teóricos y reales de los comprimidos con 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (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

Tabla 26

Materiales usados en el recubrimiento EC y sus cantidades para el lote BUP-HBr-XL-348 mg-018-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	3,42	73,57	38,00
Povidona USP (Kollidon 90F)	4,41	94,86	49,00
PEG 4000	1,17	25,17	13,00
Alcohol etílico 95 % USP	86,45	1.859,53	N/A
Alcohol isopropílico 99 % USP	4,55	97,87	N/A
Total	100,00	2.151,00	100,00

*El total de sólidos incluyó 73,57 g de Ethocel, 94,86 g de povidona y 25,17 g de PEG 4000. Esto dio una cantidad de sólidos totales de 193,6 g.

Tabla 27

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-018-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
26,0	398,0	397,7
28,0	400,0	399,5
30,0	402,0	401,5
32,0	404,0	404,0

5

Tabla 28

Materiales usados en el recubrimiento final y sus cantidades para el lote BUP-HBr-XL-348 mg-018-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	Cantidad de sólido (g)	% de sólidos en solución
Eudragit L30D D-55	22,75	104,86	31,46	65,00*
Syloid 244FP	2,62	12,08	12,08	25,00**
Carbowax 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

*El porcentaje de Eudragit, sólido, que contribuyó a la cantidad total de sólidos fue de 65 %.

**Los porcentajes de Syloid, Carbowax 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 %.

***La cantidad total de sólidos (48,4 g) fue de 10,5 % del total de la solución.

Tabla 29

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 (mg)	Peso teórico (mg)	Peso real (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 30

Materiales usados en el recubrimiento EC y sus cantidades para el lote BUP-HBr-XL-174 mg-022-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	3,60	116,12	40,00
Povidona USP (Kollidon 90F)	4,32	139,34	48,00
PEG 4000	1,08	34,84	12,00
Alcohol etílico 95 % USP	86,45	2.788,54	N/A
Alcohol isopropílico 99 % USP	4,55	146,76	N/A
Total	100,00	3.225,60	100,00

*El total de sólidos incluyó 116,12 g de Ethocel, 139,34 g de povidona y 34,84 g de PEG 4000. Esto dio una cantidad total de sólidos de 290,3g.

Tabla 31

Pesos teóricos y reales de los comprimidos con 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 29 mg y 30 mg de aumento de peso para el lote BUP-HBr-XL-174 mg-022-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (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 32

Materiales usados en el recubrimiento final y sus cantidades para el lote BUP-HBr-XL-174 mg-022-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	Cantidad de sólido (g)	% de sólidos en solución
Eudragit L30D D-55	22,75	104,86	31,46	65,0*
Syloid 244FP	2,62	12,08	12,08	25,0**
Carbowax 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

*El porcentaje de Eudragit, sólido, que contribuyó a la cantidad total de sólidos fue de 65 %.

**Los porcentajes de Syloid, Carbowax 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 %.

***La cantidad total de sólidos (48,4 g) fue de 10,5 % del total de la solución.

Tabla 33

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 (mg)	Peso teórico (mg)	Peso real (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

Tabla 34

Materiales usados en el recubrimiento EC y sus cantidades para el lote BUP-HBr-XL-348 mg-023-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	3,69	79,37	42,71
Povidona USP (Kollidon 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 etílico 95 % USP	91,00	1.957,4	N/A
Total	100,00	2.151,00	100,00

*El total de sólidos incluyó 79,37 g de Ethocel, 79,37 g de povidona y 27,11 g de PEG 4000 y 7,75 g de sebacato de dibutilo. Esto dio un total de sólidos de 193,6 g.

Tabla 35

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-023-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (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

Tabla 36

Materiales usados en el recubrimiento de EC y sus cantidades para en el lote BUP-HBr-XL-348 mg-025-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	3,69	79,40	41,00
Povidona USP (Kollidon 90F)	3,78	81,30	42,00
PEG 4000	1,53	32,90	17,00
Alcohol etílico 95 % USP	91,00	1.957,40	N/A
Total	100,00	2.151,00	100,00

*El total de sólidos incluyó 79,40g de Ethocel, 81,30g de povidona y 32,90g de PEG 4000. Esto dio una cantidad total de sólidos de 193,6g.

Tabla 37

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 (mg)	Peso teórico (mg)	Peso real (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

5

Tabla 38

Materiales usados en el recubrimiento final y sus cantidades. para el lote BUP-HBr-XL-348 mg-025-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	Cantidad de sólido (g)	% de sólidos en solución
Eudragit L30D D-55	19,77	91,13	27,34	56,50*
Syloid 244FP	3,15	14,52	14,52	30,00**
Carbowax 4000	0,95	4,36	4,36	9,00**
Citrato de trietilo	0,47	2,17	2,17	4,50**
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 de Eudragit, sólido, que contribuyó a la cantidad total de sólidos fue de 65 %.

**Los porcentajes de Syloid, Carbowax 4000 y citrato de trietilo, que contribuyeron a la cantidad total de sólidos fueron de 30 %, 9 % y 4,5 %, respectivamente. Esto dio un total de 43,5 %.

***La cantidad total de sólidos (48,39g) fue de 10,5 % del total de la solución.

Tabla 39

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 (mg)	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

Tabla 40

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-XL-348 mg-026-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	3,69	79,37	41,00
Povidona USP (Kollidon 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 etílico 95 % USP	91,00	1.957,4	N/A
Total	100,00	2.151,00	100,00

*El total de sólidos incluyó 79,37 g de Ethocel, 79,37 g de povidona, 7,75 g de PEG 4000 y 27,11 g de sebacato de dibutilo. Esto dio una cantidad total de sólidos de 193,6g.

Tabla 41

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-026-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (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

787

Tabla 42

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-XL-174 mg-027-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	3,69	138,87	41,00
Povidona USP (Kollidon 90F)	3,78	142,25	42,00
PEG 4000	1,53	57,58	17,00
Alcohol etílico 95 % USP	91,00	3.424,63	N/A
Total	100,00	3.763,33	100,00

*El total de sólidos incluyó 138,87g de Ethocel, 142,25g de povidona y 57,58g de PEG 4000. Esto dio una cantidad total de sólidos de 338,7g.

Tabla 43

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 (mg)	Peso teórico (mg)	Peso real (mg)
22,0	208,0	207,7
24,0	210,0	210,8
26,0	212,0	212,4

Tabla 44

Materiales usados en el recubrimiento final y sus cantidades para el lote BUP-HBr-XL-174 mg-027-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	Cantidad de sólido (g)	% de sólidos en solución
Eudragit L30D D-55	19,77	182,27	54,68	56,5*
Syloid 244FP	3,15	29,03	29,03	30,0**
Carbowax 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 Eudragit, sólido, que contribuyó a la cantidad total de sólidos fue de 56,5 %.

**Los porcentajes de Syloid, Carbowax 4000 y citrato de trietilo, que contribuyeron a la cantidad total de sólidos fueron de 30,0 %, 9,0 % y 4,5 %, respectivamente. Esto dio un total de 43,5 %.

***La cantidad total de sólidos (9,77 g) fue de 10,5 % del total de la solución.

Tabla 45

Pesos teóricos y reales de los comprimidos de con 4 mg, 5 mg, 6 mg y 7 mg de aumento de peso para el lote BUP-HBr-XL-174 mg-027-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (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

Tabla 46

Contenido de cada ensayo y cantidad de cada material en cada parte para la formulación EA.

Materiales	Cantidad (g)				
	Parte 1	Parte 2	Parte 3	Parte 4	Parte 5
Bupropion HBr	2.062,5	2.062,5	2.062,5	2.062,5	2.062,5
PVA	68,75	68,75	68,75	68,75	68,75
Agua purificada	1.452,5	1.452,5	1.452,5	1.452,5	1.452,5

Tabla 47

Resumen de las especificaciones para el procedimiento de granulación para las formulaciones EA.

Especificación	Ajuste/intervalos	Referencia
Velocidad del ventilador	Lenta	Lenta
Volumen de aire (CMH)	60-65	65
Temperatura de salida (° C)	35-45	40
Temperatura de alimentación (° C)	60-65	65
Temperatura del producto (° C)	35-55	45
Presión del aire de pulverización (Bar/psi)	35	35
Velocidad de bomba (rpm)	18	18
Velocidad de flujo del líquido (g/min)	13	13
Punto de rocío del lecho (MMWC)	0	0
Punto de rocío del filtro (MMWC)	100-300	200

Tabla 48

La cantidad de lubricante en la formulación EA final fue de 343,75 g, lo que constituyó 3,125 % del total.

Materiales	Cantidad (g)
Bupropion HBr en gránulos	10.656,25
Compritol 888	343,75
Total	11.000

5

Tabla 49

Resumen de especificaciones para el ajuste de la compresora de comprimidos para la formulación EA.

Parámetros	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

Tabla 50

Resumen de las especificaciones de compresión para la formulación EA.

Parámetros	Especificación para comprimido de 150 mg	Especificación para comprimido de 300 mg
Peso de cada comprimido (mg)	160,0 ± 5 % (152,0 mg-168,0 mg)	320,0 ± 5 % (304,0 mg-336,0 mg)
Peso promedio de los comprimidos (mg)	160,0 ± 3 % (155,2 mg-164,8 mg)	320,0 ±3 % (310,4 mg-329,6 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

800
786

Tabla 51

Formulaciones usadas como el recubrimiento de Ethocel en los núcleos de bupropion HBr EA de 150 mg y 300 mg.

FORMULACIÓN 1	FORMULACIÓN 2	FORMULACIÓN 3	FORMULACIÓN 4
- Ethocel (etilcelulosa) Estándar 100 Premium - Povidona USP (Kollidon 90F) - Polietilenglicol 4000 Alcohol etílico 200 de graduación	- Ethocel (etilcelulosa) Estándar 100 Premium - Povidona USP (Kollidon 90F) - Polietilenglicol 4000 - Sebacato de dibutilo Alcohol etílico 200 de graduación	- Ethocel (etilcelulosa) Estándar 100 Premium - Povidona USP (Kollidon 90F) - Sebacato de dibutilo Alcohol etílico 200 de graduación	- Ethocel (etilcelulosa) Estándar 100 Premium - Povidona USP (Kollidon 90F) - Polietilenglicol 4000 - Alcohol etílico 95 % USP

787

Tabla 52

Resumen de especificaciones que se mantuvieron constantes en el proceso de recubrimiento para las formulaciones EA.

Parámetros del proceso	Intervalos	Referencia
Temperatura de entrada para recubrimiento (° C)	SV: 50 ± 5	50
	PV: 50 ± 5	
Temperatura de entrada para secado (° C)	40 ± 5	40
Temperatura de salida	35 ± 5	35
Temperatura del producto	35 ± 2	35
Presión diferencial ΔP (W.C)	(-0,1)-(-0,12)	-0,10
Flujo de suministro de aire (CFM)	200 ± 50	200
Velocidad de la paila (rpm)	2,5-15	12,0
Aire de pulverización (psi)	25-35	35
Aire patrón (psi)	20-30	25
Velocidad de pulverización (g/min)	5-15	13

Tabla 53

Materiales usados en el lote, porcentaje de cada componente, cantidad por comprimido EA de 300 mg y cantidad por lote.

Materiales	%	mg/comprimido	Cantidad por lote (g)
Bupropion HBr	93,75	300,00	1.993,75
PVA	3,125	10,00	68,75
Compritol 888	3,125	10,00	68,75
Total	100,00	320,0 mg	2.131,25

Tabla 54

Materiales usados en el lote, porcentaje de cada componente, cantidad por comprimido EA de 150 mg y cantidad por lote.

Materiales	%	mg/comprimido	Cantidad por lote (g)
Bupropion HBr	93,75	150,00	1.993,75
PVA	3,125	5,00	68,75
Compritol 888	3,125	5,00	68,75
Total	100,00	160,0 mg	2.131,25

802
800

Tabla 55

Resultados obtenidos usando los punzones de 9 mm (formulaciones EA).

Parámetros	Teórico	Real
Peso promedio de los comprimidos	372,0 mg	371,5 mg
Dureza promedio	6,0-12,0 SC	10,77 SC
Espesor promedio	5,0-6,0 mm	5,60 mm
Friabilidad	<0,8 %	0 %

5

Tabla 56

Resultados obtenidos usando los punzones de 7 mm (formulaciones EA).

Parámetros	Teórico	Real
Peso promedio de los comprimidos	372,0 mg	366,5 mg
Dureza promedio	6,0-12,0 SC	7,50 SC
Espesor promedio	5,0-6,0 mm	4,97 mm
Friabilidad	<0,8 %	0 %

5

Tabla 57:

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-EA-300 mg-001-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución
Ethocel (etilcelulosa) estándar 100 Premium	4,94	185,62*	55,00
Povidona USP (Kollidon 90F)	2,52	94,50*	28,00
PEG 4000	0,77	28,69*	8,50
Sebacato de dibutilo	0,77	28,69*	8,50
Alcohol etílico anhidro (200 de graduación)	91,0	3.412,5	N/A
Total	100,00	3.750,00	100,00

*Los componentes sólidos totales de la formulación incluyeron todos los materiales excepto el alcohol etílico. Esta formulación constó de una cantidad total de sólidos de 337,5 g, que constituyó el 9 % del total de la solución. El 91 % restante lo constituyó el alcohol etílico de 200 de graduación (líquido).

Tabla 58

Pesos teóricos y reales de los comprimidos EA con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso para el lote BUP-HBr-EA-300 mg-001-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
44,0	364,0	362,9
46,0	366,0	365,6
48,0	368,0	366,6
50,0	370,0	369,3
52,0	372,0	371,7
54,0	374,0	374,8

Tabla 59

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-EA-150 mg-002-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución
Ethocel (etilcelulosa) estándar 100 Premium	4,94	232,03*	55,0
Povidona USP (Kollidon 90F)	2,52	118,12*	28,0
PEG 4000	0,77	35,86*	8,5
Sebacato de dibutilo	0,77	35,86*	8,5
Alcohol etílico anhidro (200 de graduación)	91,0	4.265,63	N/A
Total	100,00	4.687,50	100,00

*El total de sólidos incluyó 232,03 g de Ethocel, 118,12 g de povidona, 35,86 g de PEG 4000 y 35,86 g de sebacato de dibutilo. Esto dio una cantidad total de sólidos de 421,87g.

Tabla 60

Pesos teóricos y reales de los comprimidos con 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg y 36 mg de aumento de peso para el lote BUP-HBr-EA-150 mg-002-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
18,0	178,0	178,2
20,0	180,0	181,0
22,0	182,0	181,8
24,0	184,0	184,3
26,0	186,0	185,8
28,0	188,0	188,1
30,0	190,0	190,7
32,0	192,0	192,5
34,0	194,0	193,7
36,0	196,0	195,5

Tabla 61

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-EA-300 mg-003-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución
Ethocel (etilcelulosa) estándar 100 Premium	4,94	185,62*	55,00
Povidona USP (Kollidon 90F)	2,52	94,50*	28,00
Sebacato de dibutilo	1,54	57,38*	17,00
Alcohol etílico anhidro (200 de graduación)	91,0	3.412,5	N/A
Total	100,00	3.750,0	100,00

*El total de sólidos incluyó 185,62 g de Ethocel, 94,50 g de povidona y 57,38 g de sebacato de dibutilo. Esto dio una cantidad total de sólidos de 337,5g.

Tabla 62

Pesos teóricos y reales de los comprimidos EA con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso para el lote BUP-HBr-EA-300 mg-003-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
44,0	364,0	364,7
46,0	366,0	365,8
48,0	368,0	367,7
50,0	370,0	369,7
52,0	372,0	371,9
54,0	374,0	372,9

Tabla 63

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-EA-300 mg-004-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución
Ethocel (etilcelulosa) estándar 100 Premium	4,94	185,62*	55,00
Povidona USP (Kollidon 90F)	2,52	94,50*	28,00
PEG 4000	1,54	57,38*	17,00
Alcohol etílico anhidro (200 de graduación)	91,00	3.412,50	N/A
Total	100,00	3.750,00	100,00

*La cantidad total de sólidos incluyó 185,62 g de Ethocel, 94,50 g de povidona y 57,38 g de PEG 4000. Esto dio una cantidad de total de sólidos de 337,5 g.

Tabla 64

Pesos teóricos y reales de los comprimidos EA con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso para el lote BUP-HBr-EA-300 mg-004-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
44,0	364,0	363,6
46,0	366,0	365,5
48,0	368,0	368,5
50,0	370,0	370,2
52,0	372,0	372,6
54,0	374,0	374,3

Tabla 65

Materiales usados en el recubrimiento EC y sus cantidades para el lote BUP-HBr-EA-300-mg-005-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución
Ethocel (etilcelulosa) estándar 100 Premium	4,94	185,62*	55,00
Povidona USP (Kollidon 90F)	2,52	94,50*	28,00
PEG 4000	0,77	28,69*	8,50
Sebacato de dibutilo	0,77	28,69*	8,50
Alcohol etílico anhidro (200 de graduación)	91,00	3.412,50	N/A
Total	100,00	3.750,0	100,00

*El total de sólidos incluyó 185,62 g de Ethocel, 94,50 g de povidona, 28,69 g de PEG 4000 y 28,69 g de sebacato de dibutilo. Esto dio una cantidad total de sólidos de 337,50g. Por lo tanto, los sólidos contribuyeron en 9 % al total de la solución, y el restante 91 % lo constituyó el componente líquido (alcohol etílico anhidro).

Tabla 66

Pesos teóricos y reales de los comprimidos EA con 44 mg, 46 mg, 48 mg, 50 mg, 52 mg y 54 mg de aumento de peso para el lote BUP-HBr-EA-300 mg-005-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
44,0	364,0	364,9
46,0	366,0	366,3
48,0	368,0	368,5
50,0	370,0	371,7
52,0	372,0	372,9
54,0	374,0	373,7

Tabla 67

Materiales usados en el recubrimiento de EC y sus cantidades para el lote BUP-HBr-EA-300 mg-006-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	4,94	232,03*	55,00
Povidona USP (Kollidon 90F)	2,52	118,12*	28,00
Sebacato de dibutilo	1,54	71,72*	17,00
Alcohol etílico anhidro (200 de graduación)	91,0	4.265,63	N/A
Total	100,00	4.687,50	100,00

*El total de sólidos incluyó 232,03 g de Ethocel, 118,12 g de povidona y 71,72 g de sebacato de dibutilo. Esto dio una cantidad total de sólidos de 421,87g. El componente sólido de la solución de recubrimiento constituyó el 9 % del total de la solución. El 91 % restante lo constituyó el alcohol etílico anhidro (componente líquido).

Tabla 68

Pesos teóricos y reales de los comprimidos con 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg y 36 mg de aumento de peso para el lote BUP-HBr-EA-150 mg-006-5.

Aumento de peso (mg)	Peso teórico (mg)	Peso real (mg)
18,0	178,0	178,2
20,0	180,0	180,3
22,0	182,0	181,8
24,0	184,0	184,6
26,0	186,0	185,8
28,0	188,0	188,8
30,0	190,0	190,9
32,0	192,0	191,6
34,0	194,0	194,1
36,0	196,0	196,7

Tabla 69

Materiales usados en el recubrimiento EC y sus cantidades para el lote BUP-HBr-EA-150 mg-007-5.

Materiales	% Contribución al total de la solución	Cantidad en el lote (g)	% de sólidos en solución*
Ethocel (etilcelulosa) estándar 100 Premium	4,94	232,03	55,00
Povidona USP (Kollidon 90F)	2,52	118,12	28,00
PEG 4000	1,54	71,72	17,00
Alcohol etílico 95 % USP	91,00	4.265,63	N/A
Total	100,00	4.687,50	100,00

*El total de sólidos incluyó 232,03g de Ethocel, 118,12g de povidona y 71,72g de PEG 4000. Esto dio una cantidad total de sólidos de 421,87g.

Tabla 70

Estudios de estabilidad en vidrio de reloj sin tapar (40°C/75 % de HR) en comprimidos recubiertos con EC de bupropion HCl y bupropion HBr.

Pruebas	Inicial	Estabilidad en vidrio de reloj sin tapar (40°C/75 % de HR)	
		13 días	20 días
Comprimidos de bupropion HBr XL recubiertos con EC de 348 mg (EC-32 mg de peso), N° de lote Bup-HBr-XL-012-5 (EC-32 mg de peso)			
contenido %	101,2	99,6	99,9
% de impurezas 3-CBZ	0,021	0,056	0,067
852U77	0,029	0,350	0,486
20U78/dilu	0,054	0,046	0,047
827U76	ND	0,056	0,062
Desconocidas totales	0,356	0,059	0,123
Total	0,46	0,57	0,79
Comprimidos de bupropion HCl XL recubiertos con EC de 300 mg (EC, N° de lote 05D047)			
contenido %	100,4	100,2	96,2
% de impurezas 3-CBZ	0,015	0,089	0,117
852U77	0,041	0,337	0,378
20U78/dilu	0,038	0,046	0,045
827U76	0,023	0,071	0,080
Desconocidas totales	0,118	0,112	0,145
Total	0,24	0,66	0,77

Tabla 71

Estudios de estabilidad en vidrio de reloj sin tapar (40°C/75 % de HR) en comprimidos de bupropion HCl y bupropion HBr recubiertos con el recubrimiento final.

Pruebas	Inicial	Comprimidos recubiertos de bupropion HBr XL de 348 mg (peso final 8 mg), N° de lote Bup-HBr-XL-012-5 (EC32 mg de peso - peso final 8 mg)		Inicial	Comprimidos de Wellbutrin (Bupropion HCl) XL de 300 mg N° de lote 05A116	
		13 días	20 días		13 días	20 días
contenido %	97,7	103,0	98,6	98,1	95,6	95,5
% de impurezas						
3-CBZ	0,021	0,091	0,119	0,032	0,171	0,279
852U77	0,039	0,505	0,412	0,193	0,974	1,228
20U78/dilu	0,051	0,055	0,048	0,042	0,055	0,062
827U76	ND	0,046	0,054	0,028	0,082	0,096
Desconocidas totales	0,476	0,110	0,112	0,083	0,033	0,06
Total (%)	0,58	0,80	0,75	0,38	1,32	1,73

Tabla 72

Peso promedio de excipientes y peso del IFA presente en las muestras de degradación forzada para el Ejemplo 8

Componente	Peso promedio en mg presente en las muestras usadas para el estudio de degradación forzada	
IFA	348 -HBr	350 - HCl
Precirol	162	
Manitol	413	
Avicel pH101	154	
L-HPC	20	
Kollidon	20	
Ácido cítrico	31	
Etilcelulosa E45	54	
ATBC	16	

Tabla 73

FORMULACIÓN DE LA SOLUCIÓN DE RECUBRIMIENTO PARA BUPROPION HBr EA / mg /COMPRIMIDO PARA LOTES FUNDAMENTALES

Comprimidos EA recubiertos de 150 mg - Formulación de recubrimiento fundamental / Tamaño del lote				
N° de artículo	Material	Cant. necesaria (kg)	% del lote	mg/comprimido
RE0233	Etilcelulosa 100, NF	4,210	4,95 %	19,80
RE0067	Povidona, USP	2,140	2,52 %	10,06
RE0331	Polietilenglicol 4000, NF	0,435	0,51 %	2,05
RE0103	Sebacato de dibutilo, NF	0,870	1,02 %	4,09
RS0010	Alcohol deshidratado, 200 de graduación, USP	73,475	86,44 %	N/A
RS0006	Alcohol etílico, 95 % USP	3,870	4,56 %	N/A
TOTAL DE SOLUCIÓN DE RECUBRIMIENTO (kg)		85 kg	100 %	36 mg Intervalo (38-40 mg)
*RE0223	Cera carnauba, NF	0,010 kg	N/A	0,05 mg/comprimido
Comprimidos EA recubiertos de 300 mg - Formulación de recubrimiento fundamental / Tamaño del lote				
N° de artículo	Material	Cant. necesaria (kg)	% del lote	mg/comprimido
RE0233	Etilcelulosa 100, NF	5,450	4,95 %	23,12
RE0067	Povidona, USP	2,770	2,52 %	11,75
RE0331	Polietilenglicol 4000, NF	0,560	0,51 %	2,38
RE0103	Sebacato de dibutilo, NF	1,120	1,02 %	4,75
RS0010	Alcohol deshidratado, 200 de graduación, USP	95,070	86,43 %	N/A
RS0006	Alcohol etílico, 95 % USP	5,030	4,57 %	N/A
TOTAL DE SOLUCIÓN DE RECUBRIMIENTO (kg)		110 kg	100 %	42 mg/comprimido Intervalo (40-44 mg)
*RE0223	Cera carnauba, NF	0,010 kg	N/A	0,05 mg/comprimido

Nota: En los casos en que fue pertinente, los porcentajes y los totales de mg/comprimido se redondearon a dos cifras decimales.

*La cera carnauba no se incluyó como parte de la formulación de la solución de recubrimiento. Se aplicaron trazas después de completar el proceso de recubrimiento.

Las referencias a patentes y otros documentos citados en las especificaciones de esta patente se incorporan por referencia en su totalidad en la medida en que sus divulgaciones no sean incongruentes con los enseñanzas explícitas o implícitas de esta solicitud especialmente las definiciones.

TABLA 74

PROGRAMA DE ESTABILIDAD ACELERADA				
Producto: Bupropion HBr FV0092	N° de lote: D00894	Fecha de inicio: 20/12/04	Temperatura: 40°C ± 2°C H.R.: 75 % ± 5 %	
Análisis	Especificación	tiempo 0	3 meses	6 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva
Contenido de agua (K.F.)	NMD 0,5 %	0,05	0,07	0,08
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,06	4) 0,04 5) n.c. 6) 0,02
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,6	99,6	99,7

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

TABLA 75

PROGRAMA DE ESTABILIDAD ACELERADA				
Producto: Bupropion HBr FV0092	N° de lote: D00895	Fecha de inicio: 20/12/04	Temperatura: 40°C ± 2°C H.R.: 75 % ± 5 %	
Análisis	Especificación	tiempo 0	3 meses	6 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva
Contenido de agua (K.F.)	NMD 0,5 %	0,04	0,07	0,07
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) 0,05	1) 0,05 2) n.d. 3) n.c.
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,05	4) 0,04 5) n.c. 6) 0,02
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,2	100,7	99,7

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

TABLA 76

PROGRAMA DE ESTABILIDAD ACELERADA				
Producto: Bupropion HBr FV0092	N° de lote: D00896	Fecha de inicio: 20/12/04	Temperatura: 40°C ± 2°C H.R.: 75 % ± 5 %	
Análisis	Especificación	tiempo 0	3 meses	6 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva
Contenido de agua (K.F.)	NMD 0,5 %	0,06	0,11	0,04
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,05 6) 0,05	4) 0,03 5) 0,04 6) 0,05	4) 0,04 5) n.c. 6) n.c.
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,3	100,0	100,4

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

TABLA 77

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL									
Producto: Bupropion HBr FV0092	N° de lote: D00894			Fecha de inicio: 20/12/04			Temperatura: 25° C ± 2° C Humedad relativa: 60 % ± 5 %		
Análisis	Especificación	tiempo 0	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple	cumple	cumple			
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva	positiva	positiva			
Contenido de agua (K.F.)	NMD 0,5 %	0,05	0,05	0,06	0,05	0,05			
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) n.d. 2) n.d. 3) 0,05	1) 2) 3)	1) 2) 3)	1) 2) 3)
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,05	4) 0,05 5) n.c. 6) 0,02	4) n.d. 5) n.c. 6) n.c.	4) 0,05 5) 0,05 6) 0,07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1	n.c.	0,2			
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,6	99,4	100,2	99,5	99,6			
Contenido microbiológico	• recuento microbiológico total < 1000 ufc/g • hongos y levaduras < 100 ufc/g	no se aplicó	no se aplicó	no se aplicó	no se aplicó	< 100 ufc/g < 100 ufc/g	no se aplicó		

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

TABLA 78

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL									
Producto: Bupropion HBr FV0092	N° de lote: D00895			Fecha de inicio: 20/12/04			Temperatura: 25° C ± 2° C Humedad relativa: 60 % ± 5 %		
Análisis	Especificación	tiempo 0	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple	cumple	cumple			
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva	positiva	positiva			
Contenido de agua (K.F.)	NMD 0,5 %	0,04	0,04	0,05	0,05	0,04			
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) n.d. 2) n.d. 3) 0,05	1) 2) 3)	1) 2) 3)	1) 2) 3)
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,05	4) 0,05 5) n.c. 6) 0,02	4) n.d. 5) n.c. 6) n.c.	4) 0,05 5) 0,07 6) 0,07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1	n.c.	0,2			
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,2	99,5	100,1	99,4	99,4			
Contenido microbiológico	• recuento microbiológico total < 1000 ufc/g • hongos y levaduras < 100 ufc/g	no se aplicó	no se aplicó	no se aplicó	no se aplicó	< 100 ufc/g < 100 ufc/g	no se aplicó		

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

TABLA 79

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL									
Producto: Bupropion HBr FV0092	N° de lote: D00896			Fecha de inicio: 20/12/04			Temperatura: 25° C ± 2° C Humedad relativa: 60 % ± 5 %		
Análisis	Especificación	tiempo 0	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple	cumple	cumple			
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva	positiva	positiva			
Contenido de agua (K.F.)	NMD 0,5 %	0,06	0,04	0,04	0,04	0,03			
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) n.d. 2) n.d. 3) n.c.	1) 2) 3)	1) 2) 3)	1) 2) 3)
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,05 6) 0,05	4) 0,03 5) 0,04 6) 0,05	4) 0,04 5) n.c. 6) n.c.	4) n.d. 5) n.c. 6) n.c.	4) 0,05 5) 0,07 6) 0,07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1	n.c.	0,1			
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,3	99,4	100,5	99,4	100,3			
Contenido microbiológico	• recuento microbiológico total < 1000 ufc/g • hongos y levaduras < 100 ufc/g	no se aplicó	no se aplicó	no se aplicó	no se aplicó	< 100 ufc/g < 100 ufc/g	no se aplicó		

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

Tabla 80

Tabla de polimorfos del bromhidrato de bupropion

Ensayo	Disolvente (vol.)	Co-disolvente (vol.)	Rendimiento (%)	Forma	K.F. (%)	Notas
085	AIP + HBr gas			I	0,07	procedimiento estándar
097	Agua 2	/	72	I	0,06	
098A	Metanol 2,4	/		II	0,13	
098B	Acetona 17	Agua 0,7	24	II	0,16	
099	Etanol abs. 4,8	/	56	III	0,12	
100	AIP 15,1	/	77	I	0,11	
102	AcOi-Pr 20	MeOH 3,6	26	I	0,25	
108	Acetonitrilo 20	/	70	I	0,14	
109	Diclorometano 30	/	25	II	0,21	
110	Agua 2	HBr 48 % 1	83	I	0,12	
111	AIP 6	HBr 48 % 1	69	I	0,32	
112	MTBE 10	MeOH 3	67	I	0,18	
113	Tolueno 10	MeOH 1,25	40	II	0,39	
114	DMC 10	MeOH 1,75	67	II	0,17	
115	t-BuOH 20	Agua 0,55	74	I	0,15	
116	Forma I en el rotavapor 100° C 24 h			I	0,45	
117	AIP 10	Agua 0,125	88	I	0,32	
118	Tolueno 10	MeOH 1,15	99	I	0,16	
119	AIP 8	MeOH 1,32	83	I	0,47	
120	sec-BuOH 25	/	89	I	0,13	
122	Agua 8	/		I	1,3	Secado por aspersión

TABLA 81

Ácidos grasos polietoxilados

Aunque el polietilenglicol (PEG) en sí mismo no actúa como un tensioactivo, hay diversos ésteres de ácidos grasos de PEG que tienen propiedades tensioactivas útiles. En la Tabla 81 se muestran ejemplos de monoésteres de ácidos grasos polietoxilados tensioactivos disponibles en el comercio.

Tensioactivos monoésteres de ácidos grasos de PEG		
Compuesto	Producto comercial (proveedor)	EHL
monolaurato de PEG 4-100	Serie Crodet L (Croda)	>9
monooleato de PEG 4-100	Serie Crodet O (Croda)	>8
monoestearato de PEG 4-100	Serie Crodet S (Croda), serie Myrj (Atlas/ICI)	>6
diestearato de PEG 400	Serie Cithrol 4SF (Croda)	>10
monolaurato de PEG 100, 200, 300	Serie Cithrol ML (Croda)	>10
monooleato de PEG 100, 200, 300	Serie Cithrol MO (Croda)	>10
dioleato de PEG 400	Serie Cithrol 4DO (Croda)	>10
monoestearato de PEG 400-1000	Serie Cithrol MS (Croda)	>10
estearato de PEG-1	Nikkol MYS-IEX (Nikko), Coster KI (Condea)	2
estearato de PEG-2	Nikkol MYS-2 (Nikko)	4
oleato de PEG -2	Nikkol MYO-2 (Nikko)	4,5
laurato de PEG-4	Mapeg® 200 ML (PPG), Kessco® PEG 200ML (Stepan), LIPOPEG 2L (LIPO Chem.)	9,3
oleato de PEG -4	Mapeg® 200 MO (PPG), Kessco® PEG200 MO (Stepan),	8,3
estearato de PEG-4	Kessco® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6,5
estearato de PEG-5	Nikkol TMGS-5 (Nikko)	9,5
oleato de PEG -5	Nikkol TMGO-5 (Nikko)	9,5
oleato de PEG -6	Algon OL 60 (Auschem SpA), Kessco® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8,5
oleato de PEG -7	Algon OL 70 (Auschem SpA)	10,4
laurato de PEG-6	Kessco® PEG300 ML (Stepan)	11,4
laurato de PEG-7	Lauridac 7 (Condea)	13
estearato de PEG-6	Kessco® PEG300 MS (Stepan)	9,7

Tensioactivos monoésteres de ácidos grasos de PEG		
Compuesto	Producto comercial (proveedor)	EHL
laurato de PEG-8	Mapeg® 400 ML (PPG), LIPOPEG 4DL (Lipo Chem.)	13
oleato de PEG-8	Mapeg® 400 MO (PPG), Emulgante A8 (Condea); Kessco PEG 400 MO (Stepan)	12
estearato de PEG-8	Mapeg® 400 MS (PPG), Myrj 45	12
oleato de PEG-9	Emulgante A9 (Condea)	>10
estearato de PEG-9	Cremophor 59 (BASF)	>10
laurato de PEG-10	Nikkol MYL-10 (Nikko), Lauridac 10 (Croda)	13
oleato de PEG-10	Nikkol MYO-10 (Nikko)	11
estearato de PEG-10	Nikkol MYS-10 (Nikko), Coster K100 (Condea)	11
laurato de PEG-12	Kessco® PEG 600ML (Stepan)	15
oleato de PEG-12	Kessco® PEG 600MO (Stepan)	14
ricinoleato de PEG-12	(CAS #9004-97-1)	>10
estearato de PEG-12	Mapeg® 600 MS (PPG), Kessco® PEG 600MS (Stepan)	14
estearato de PEG-15	Nikkol TMGS-15 (Nikko), Koster K15 (Condea)	14
oleato de PEG-15	Nikkol TMGO-15 (Nikko)	15
laurato de PEG-20	Kessco® PEG 1000 ML (Stepan)	17
oleato de PEG-20	Kessco® PEG 1000 MO (Stepan)	15
estearato de PEG-20	Mapeg® 1000 MS (PPG), Kessco® PEG 1000 MS (Stepan), Myrj 49	16
estearato de PEG-25	Nikkol MYS-25 (Nikko)	15
laurato de PEG-32	Kessco® PEG 1540 ML (Stepan)	16
oleato de PEG-32	Kessco® PEG 1540 MO (Stepan)	17
estearato de PEG-32	Kessco® PEG 1540 MS (Stepan)	17
estearato de PEG-30	Myrj 51	>10
laurato de PEG-40	Crodet L40 (Croda)	17,9
oleato de PEG-40	Crodet O40 (Croda)	17,4
estearato de PEG-40	Myrj 52, Emerest® 2715 (Henkel), Nikkol MYS-40 (Nikko)	>10
estearato de PEG-45	Nikkol MYS-45 (Nikko)	18
estearato de PEG-50	Myrj 53	>10
estearato de PEG-55	Nikkol MYS-55 (Nikko)	18
oleato de PEG-100	Crodet O-100 (Croda)	18,8
estearato de PEG-100	Myrj 59, Arlacel 165 (ICI)	19
oleato de PEG-200	Albunol 200 MO (Taiwan Surf.)	>10
oleato de PEG-400	LACTOMUL (Henkel), Albunol 400 MO (Taiwan Surf.)	>10
oleato de PEG-600	Albunol 600 MO (Taiwan Surf)	>10

TABLA 82

Diésteres de ácidos grasos de PEG

Los diésteres de ácidos grasos de polietilenglicol (PEG) también son adecuados para usar como tensioactivos en las composiciones de la presente invención. En la Tabla 82 se muestran diésteres de ácidos grasos de PEG representativos.

Tensioactivos diésteres de ácidos grasos de PEG		
Compuesto	Producto comercial (proveedor)	EHL
dilaurato de PEG-4	Mapeg® 200 DL (PPG), Kessco® PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7 6
dioleato de PEG-4	Mapeg® 200 DO (PPG),	6
diestearato de PEG-4	Kessco® 200 SF (Stepan)	5
dilaurato de PEG-6	Kessco® PEG 300 DL (Stepan)	9,8
dioleato de PEG-6	Kessco® PEG 300 DO (Stepan)	7,2
diestearato de PEG-6	Kessco® PEG 300 SF (Stepan)	6,5
dilaurato de PEG-8	Mapeg® 400 DL (PPG), Kessco® PEG 400 DL (Stepan), LIPOPEG 4 DL (Lipo Chem.)	11
dioleato de PEG-8	Mapeg® 400 DO (PPG), Kessco® PEG 400 DO (Stepan), LIPOPEG 4 DO (Lipo Chem.)	8,8
diestearato de PEG-8	Mapeg® 400 SF (PPG), CSF 400 (Nikkol)	11
dipalmitato de PEG-10	Polyaldo 2PKFG	>10
dilaurato de PEG-12	Kessco® PEG 600 DL (Stepan)	11,7
diestearato de PEG-12	Kessco® PEG 600 SF (Stepan)	10,7
dioleato de PEG-12	Mapeg® 600 DO (PPG), Kessco® 600 DO(Stepan)	10
dilaurato de PEG-20	Kessco® PEG 1000 DL (Stepan)	15
dioleato de PEG-20	Kessco® PEG 1000 DO (Stepan)	13
diestearato de PEG-20	Kessco® PEG 1000 SF (Stepan)	12
dilaurato de PEG-32	Kessco® PEG 1540 DL (Stepan)	16
dioleato de PEG-32	Kessco® PEG 1540 DO (Stepan)	15
diestearato de PEG-32	Kessco® PEG 1540 SF (Stepan)	15
dioleato de PEG-400	Serie Cithrol 4DO (Croda)	>10
diestearato de PEG-400	Serie Cithrol 4SF (Croda)	>10

TABLA 83

Mezclas de mono y di ésteres de ácidos grasos de PEG

En general, las mezclas de tensioactivos también son útiles en la presente invención, incluidas mezclas de dos o más productos tensioactivos comerciales. Varios ésteres de ácidos grasos de PEG se comercializan como mezclas de mono y di ésteres. En la Tabla 83 se muestran ejemplos de mezclas representativas de tensioactivos.

Tensioactivos mono y di ésteres de ácidos grasos de PEG	
Compuesto	Producto comercial (proveedor)
mono, dilaurato de PEG 4-150	Kessco® PEG 200-6000 mono, dilaurato (Stepan)
mono, dioleato de PEG 4-150	Kessco® PEG 200-6000 mono, dioleato (Stepan)
mono, diestearato de PEG 4-150	Kessco® PEG 200-6000 mono, diestearato (Stepan)

TABLA 84

Ésteres de ácidos grasos de glicerol con PEG

En la Tabla 84 se muestran ésteres de ácidos grasos de glicerol con PEG adecuados.

Ésteres de ácidos grasos de glicerol con PEG		
Compuesto	Producto comercial (proveedor)	EHL
PEG 20 laurato de glicerilo	Tagat® L (Goldschmidt)	16
PEG-30 laurato de glicerilo	Tagat® L2 (Goldschmidt)	16
PEG-15 laurato de glicerilo	serie Glycerox L (Croda)	15
PEG-40 laurato de glicerilo	serie Glycerox L (Croda)	15
PEG-20 estearato de glicerilo	Capmul® EMG (ABITEC), Aldo® MS-20 KFG (Lonza)	13
PEG-20 oleato de glicerilo	Tagat® O (Goldschmidt)	>10
PEG-30 oleato de glicerilo	Tagat® O2 (Goldschmidt)	>10

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TABLA 85

Productos de Transesterificación aceite-alcohol

Se puede preparar una gran cantidad de tensioactivos de diferentes grados de lipofilicidad o hidrofilicidad mediante la reacción de alcoholes o polioles con una diversidad de aceites naturales y/o hidrogenados. En ciertas realizaciones, los aceites usados son aceite de ricino o aceite de ricino hidrogenado o un aceite vegetal comestible como aceite de maíz, aceite de oliva, aceite de maní, aceite de almendra de palma, el aceite de grano de albaricoque o aceite de almendra. Los ejemplos de alcoholes incluyen glicerol, propilenglicol, etilenglicol, polietilenglicol, sorbitol y pentaeritritol. En la tabla 85 se muestran tensioactivos representativos de esta clase adecuados para usar en la presente invención.

Productos de transesterificación de aceites y alcoholes		
Compuesto	**Producto comercial (proveedor)**	**EHL**
PEG-3 aceite de ricino	Nikkol CO-3 (Nikko)	3
PEG-5,9 y 16 aceite de ricino	ACCONON CA series (ABITEC)	6-7
PEG-20 aceite de ricino	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
PEG-23 aceite de ricino	Emulgante EL23	>10
PEG-30 aceite de ricino	Emalex C-30 (Nihon Emulsion), Alkamuls® EL 620 (Rhone-Poulenc), Incrocas 30 (Croda)	11
PEG-35 aceite de ricino	Cremophor EL y EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 aceite de ricino	Emulgante EL 65 (Condea)	
PEG-40 aceite de ricino	Emalex C-40 (Nihon Emulsion), Alkamuls® EL 719 (Rhone-Poulenc)	13
PEG-50 aceite de ricino	Emalex C-50 (Nihon Emulsion)	14
PEG-56 aceite de ricino	Eumulgin® PRT 56 (Pulcra SA)	>10
PEG-60 aceite de	Nikkol CO-60TX (Nikko)	14

Productos de transesterificación de aceites y alcoholes		
Compuesto	**Producto comercial (proveedor)**	**EHL**
ricino		
PEG-100 aceite de ricino	Thornley	>10
PEG-200 aceite de ricino	Eumulgin® PRT 200 (Pulcra SA)	>10
PEG-5 aceite de ricino hidrogenado	Nikkol HCO-5 (Nikko)	6
PEG-7 aceite de ricino hidrogenado	Simusol® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 aceite de ricino hidrogenado	Nikkol HCO-10 (Nikko)	6,5
PEG-20 aceite de ricino hidrogenado	Nikkol HCO-20 (Nikko)	11
PEG-25 aceite de ricino hidrogenado	Simulsol® 1292 (Seppic), Cerex ELS 250 (Auschem SpA)	11
PEG-30 aceite de ricino hidrogenado	Nikkol HCO-30 (Nikko)	11
PEG-40 aceite de ricino hidrogenado	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
PEG-45 aceite de ricino hidrogenado	Cerex ELS 450 (Auschem Spa)	14
PEG-50 aceite de ricino hidrogenado	Emalex HC-50 (Nihon Emulsion)	14
PEG-60 aceite de ricino hidrogenado	Nikkol HCO-60 (Nikko), Cremophor RH 60 (BASF)	15
PEG-80 aceite de ricino hidrogenado	Nikkol HCO-80 (Nikko)	15
PEG-100 aceite de ricino hidrogenado	Nikkol HCO-100 (Nikko)	17
PEG-6 aceite de maíz	Labrafil® M 2125 CS (Gattefosse)	4
PEG-6 aceite de almendra	Labrafil® M 1966 CS (Gattefosse)	4
PEG-6 aceite de grano de albaricoque	Labrafil® M 1944 CS (Gattefosse)	4
PEG-6 aceite de oliva	Labrafil® M 1980 CS (Gattefosse)	4
PEG-6 aceite de maní	Labrafil® M 1969 CS (Gattefosse)	4

Productos de transesterificación de aceites y alcoholes		
Compuesto	**Producto comercial (proveedor)**	**EHL**
PEG-6 aceite de almendra de palma hidrogenado	Labrafil® M 2130 BS (Gattefosse)	4
PEG-6 aceite de almendra de palma	Labrafil® M 2130 CS (Gattefosse)	4
PEG-6 trioleína	Labrafil® M 2735 CS (Gattefosse)	4
PEG-8 aceite de maíz	Labrafil® WL 2609 BS (Gattefosse)	6-7
PEG-20 glicéridos de maíz	Crovol M40 (Croda)	10
PEG-20 glicéridos de almendras	Crovol A40 (Croda)	10
PEG-25 trioleato	TAGAT® TO (Goldschmidt)	11
PEG-40 aceite de almendra de palma	Crovol PK-70	>10
PEG-60 glicéridos de maíz	Crovol M70 (Croda)	15
PEG-60 glicéridos de almendras	Crovol A70 (Croda)	15
PEG-4 triglicéridos de caprílico/cáprico	Labrafac® Hydro (Gattefosse)	4-5
PEG-8 glicéridos de caprílico/cáprico	Labrasol (Gattefosse), Labrafac CM 10 (Gattefosse)	>10
PEG-6 glicéridos de caprílico/cáprico	SOFTIGEN® 767 (Huls), Glycerox 767 (Croda)	19
Glicérido de lauroil macrogol 32	GELUCIRE 44/14 (Gattefosse)	14
Glicérido de estearoil macrogol	GELUCIRE 50/13 (Gattefosse)	13
Mono, di, tri, tetra ésteres de aceites vegetales y sorbitol	SorbitoGlyceride (Gattefosse)	<10
Tetraisoestearato de pentaeritritol	Crodamol PTIS (Croda)	<10
Diestearato de	Albunol DS (Taiwan Surf.)	<10

Productos de transesterificación de aceites y alcoholes		
Compuesto	**Producto comercial (proveedor)**	**EHL**
pentaeritritol		
Tetraoleato de pentaeritritol	Liponate PO-4 (Lipo Chem.)	<10
Tetraestearato de pentaeritritol	Liponate PS-4 (Lipo Chem.)	<10
Tetracaprilato/tetracaprato de pentaeritritol	Liponate PE-810 (Lipo Chem.), Crodamol PTC (Croda)	<10
Tetraoctanoato de pentaeritritol	Nikkol Pentarate 408 (Nikko)	

TABLA 86

Ácidos grasos poliglicerizados

Los ésteres de ácidos grasos de poliglicerol también son tensioactivos adecuados para la presente invención. En la tabla 86 se muestran ejemplos de ésteres de poliglicerilo adecuados.

Ácidos grasos poliglicerizados		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Estearato de poliglicerilo-2	Nikkol DGMS (Nikko)	5-7
Oleato de poliglicerilo-2	Nikkol DGMO (Nikko)	5-7
Isoestearato de poliglicerilo-2	Nikkol DGMIS (Nikko)	5-7
Oleato de poliglicerilo-3	Caprol® 3GO (ABITEC), Drewpol 3-1-O (Stepan)	6,5
Oleato de poliglicerilo-4	Nikkol Tetraglyn 1-O (Nikko)	5-7
Estearato de poliglicerilo-4	Nikkol Tetraglyn 1-S (Nikko)	5-6
Oleato de poliglicerilo-6	Drewpol 6-1-O (Stepan), Nikkol Hexaglyn 1-O (Nikko)	9
Laurato de poliglicerilo-10	Nikkol Decaglyn 1-L (Nikko)	15
Oleato de poliglicerilo-10	Nikkol Decaglyn 1-O (Nikko)	14
Estearato de poliglicerilo-10	Nikkol Decaglyn 1-S (Nikko)	12
Ricinoleato de poliglicerilo-6	Nikkol Hexaglyn PR-15 (Nikko)	
Linoleato de poliglicerilo-10	Nikkol Decaglyn I-LN (Nikko)	12
Pentaoleato de poliglicerilo-6	Nikkol Hexaglyn S-O (Nikko)	<10
Dioleato de poliglicerilo-3	Cremophor G032 (BASF)	<10
Diestearato de poliglicerilo-3	Cremophor GS32 (BASF)	<10
Pentaoleato de poliglicerilo-4	Nikkol Tetraglyn 5-O (Nikko)	<10
Dioleato de poliglicerilo-6	Caprol® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8,5

Ácidos grasos poliglicerizados		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Dioleato de poliglicerilo-2	Nikkol DGDO (Nikko)	7
Trioleato de poliglicerilo-10	Nikkol Decaglyn 3-O (Nikko)	7
Pentaoleato de poliglicerilo-10	Nikkol Decaglyn 5-O (Nikko)	3,5
Septaoleato de poliglicerilo-10	Nikkol Decaglyn 7-O (Nikko)	3
Tetraoleato de poliglicerilo-10	Caprol® 10G40 (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6,2
Decaisoestearato de poliglicerilo-10	Nikkol Decaglyn 10-IS (Nikko)	<10
Decaoleato de poliglicerilo-10	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3,5
Mono, dioleato de poliglicerilo-10	Caprol® PGE 860 (ABITEC)	11
Polirricinoleato de poliglicerilo	Polymuls (Henkel)	3-20

TABLA 87

Ésteres de ácidos grasos de propilenglicol

Los ésteres de ácidos grasos de propilenglicol son tensioactivos adecuados para usar en la presente invención. En la tabla 87 se dan ejemplos de tensioactivos de esta clase.

Ésteres de ácidos grasos de propilenglicol		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Monocaprilato de propilenglicol	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
Monolaurato de propilenglicol	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
Oleato de propilenglicol	Lutrol OP2000 (BASF)	<10
Miristato de propilenglicol	Mirpyl	<10
Monoestearato de propilenglicol	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo® PGHMS (Lonza)	3-4
Hidroxiestearato de propilenglicol		<10
Ricinoleato de propilenglicol	PROPYMULS (Henkel)	<10
Isoestearato de propilenglicol		<10
Monooleato de propilenglicol	Myverol P-06 (Eastman)	<10
Dicaprilato/dicaprato de propilenglicol	Captex® 200 (ABITEC), Miglyol® 840 (Huls), Neobee® M-20 (Stepan)	>6
Dioctanoato de propilenglicol	Captex® 800 (ABITEC)	
Caprilato/caprato de propilenglicol	LABRAFAC PG (Gattefosse)	>6
Dilaurato de propilenglicol		>6
Diestearato de propilenglicol	Kessco® PGDS (Stepan)	>6
Dicaprilato de propilenglicol	Nikkol Sefsol 228 (Nikko)	>6
Dicaprato de propilenglicol	Nikkol PDD (Nikko)	>6

TABLA 88

Mezclas de ésteres de propilenglicol - ésteres de glicerol

En general, las mezclas de tensioactivos también son adecuadas para usar en la presente invención. En particular, las mezclas de ésteres de ácidos grasos de propilenglicol y ésteres de ácidos grasos de glicerol son adecuadas y están disponibles comercialmente. En la tabla 88 se muestran ejemplos de estos tensioactivos.

Ésteres de ácidos grasos de glicerol / propilenglicol		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Oleico	ATMOS 300, ARLACEL 186 (ICI)	3-4
Esteárico	ATMOS 150	3-4

TABLA 89

Mono y diglicéridos

Otra clase de tensioactivos es la clase de los mono y diglicéridos. Estos tensioactivos generalmente son lipófilos. En la Tabla 89 se dan ejemplos de estos tensioactivos.

Tensioactivos mono y diglicéridos		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Monopalmitoleína (C16:1)	(Larodan)	<10
Monoelaidina (C18:1)	(Larodan)	<10
Monocaproína (C6)	(Larodan)	<10
Monocaprilina	(Larodan)	<10
Monocaprina	(Larodan)	<10
Monolaurina	(Larodan)	<10
Monomiristato de glicerilo (C14)	Nikkol MGM (Nikko)	3-4
Monooleato de glicerilo (C18:1)	PECEOL (Gattefosse), Hodag GMO-D, Nikkol MGO (Nikko)	3-4
Monooleato de glicerilo	Serie RYLO (Danisco), serie DIMODAN (Danisco), EMULDAN (Danisco), ALDO® MO FG (Lonza), Kessco GMO (Stepan), serie MONOMULS® (Henkel), TEGIN O, DREWMULSE GMO (Stepan), Atlas G-695 (ICI), GMOrphic 80 (Eastman), ADM DMG-40, 70, y 100 (ADM), Myverol (Eastman)	3-4
Monooleato / linoleato de glicerol	OLICINE (Gattefosse)	3-4
Monolinoleato de glicerol	Maisine (Gattefosse), MYVEROL 18-92, Myverol 18-06 (Eastman)	3-4
Ricinoleato de glicerilo	Softigen® 701 (Huls), HODAG GMR-D (Calgene), ALDO® MR (Lonza)	6
Monolaurato de glicerilo	ALDO® MLD (Lonza), Hodag GML (Calgene)	6,8
Monopalmitato de	Emalex GMS-P (Nihon)	4

Tensioactivos mono y diglicéridos		
Compuesto	**Producto comercial (proveedor)**	**EHL**
glicerol		
Monoestearato de glicerol	Capmul® GMS. (ABITEC), Myvaplex (Eastman), IMWITOR® 191 (Huls), CUTINA GMS, Aldo® MS (Lonza), Nikkol MGS series (Nikko)	5-9
Mono, dioleato de glicerilo	Capmul® GMO-K (ABITEC)	<10
Palmitato/estearato de glicerilo	CUTINA MD-A, ESTAGEL-G18	<10
Acetato de glicerilo	Lamegin® EE (Grunau GmbH)	<10
Laurato de glicerilo	Inwitor® 312 (Huls), Monomuls® 90-45 (Grunau GmbH), Aldo® MLD (Lonza)	4
Citrato/lactato/oleato/linoleato de glicerilo	Imwitor® 375 (Huls)	<10
Caprilato de glicerilo	Imwitor® 308 (Huls), Capmul® MCMC8 (ABITEC)	5-6
Caprilato/caprato de glicerilo	Capmul® MCM (ABITEC)	5-6
Mono, diglicéridos del ácido caprílico	Imwitor® 988 (Huls)	5-6
Glicéridos de caprílico/ Cáprico	Imwitor® 742 (Huls)	<10
Monoglicéridos mono y diacetilados	Myvacet® 9-45, Myvacet® 9-40, Myvacet® 9-08 (Eastman), Lamegin® (Grunau)	3,8-4
Monoestearato de glicerilo	Aldo® MS, Arlacel 129 (ICI), LIPO GMS (Lipo Chem.), Imwitor® 191 (Huls), Myvaplex (Eastman)	4,4
Ésteres de mono y diglicéridos del ácido láctico	LAMEGIN GLP (Henkel)	<10
Dicaproína (C6)	(Larodan)	<10
Dicaprina (C10)	(Larodan)	<10
Dioctanoína (C8)	(Larodan)	<10

Tensioactivos mono y diglicéridos		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Dimiristina (C14)	(Larodan)	<10
Dipalmitina (C16)	(Larodan)	
Diestearina	(Larodan)	<10
Dilaurato de glicerilo (C12)	Capmul® GDL (ABITEC)	3-4
Dioleato de glicerilo	Capmul® GDO (ABITEC)	3-4
Ésteres de ácidos grasos de glicerol	GELUCIRE 39/01 (Gattefosse), GELUCIRE 43/01 (Gattefosse) GELUCIRE 37/06 (Gattefosse)	1 6
Dipalmitoleína (C16:1) 1,2 y 1,3-dioleína (C18:1)	(Larodan)	<10
Dielaidina (C18:1)	(Larodan)	<10
Dilinoleína (C18:2)	(Larodan)	<10

TABLA 90

Esterol y derivados del esterol

Los esteroles y los derivados de los esteroles son tensioactivos adecuados para usar en la presente invención. Estos tensioactivos pueden ser hidrófilos o lipófilos. En la tabla 90 se muestran ejemplos de tensioactivos de esta clase.

Tensioactivos de esterol y derivados del esterol		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Colesterol, sitosterol, lanosterol		<10
PEG-24 éter de colesterol	Solulan C-24 (Amerchol)	>10
PEG-30 colestanol	Nikkol DHC (Nikko)	>10
Fitosterol	Serie GENEROL (Henkel)	<10
PEG-25 fitoesterol	Nikkol BPSH-25 (Nikko)	>10
PEG-5 esterol de soja	Nikkol BPS-S (Nikko)	<10
PEG-10 esterol de soja	Nikkol BPS-10 (Nikko)	<10
PEG-20 esterol de soja	Nikkol BPS-20 (Nikko)	<10
PEG-30 esterol de soja	Nikkol BPS-30 (Nikko)	>10

TABLA 91

Ésteres de ácidos grasos de polietilenglicol y sorbitán

Se dispone de una diversidad de ésteres de ácidos grasos de PEG-sorbitán que son adecuados para usar como tensioactivos en la presente invención. En general, estos tensioactivos son hidrófilos, aunque se pueden usar varios tensioactivos lipófilos de esta clase. En la tabla 91 se muestran ejemplos de estos tensioactivos.

Ésteres de ácidos grasos de PEG-sorbitán		
Compuesto	**Producto comercial (proveedor)**	**EHL**
PEG-10 laurato de sorbitán	Liposorb L-10 (Lipo Chem.)	>10
PEG-20 monolaurato de sorbitán	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
PEG-4 monolaurato de sorbitán	Tween-21 (Atlas/ICI), Crillet 11 (Croda)	13
PEG-80 monolaurato de sorbitán	Hodag PSML-80 (Calgene); T-Maz 28	>10
PEG-6 monolaurato de sorbitán	Nikkol GL-1 (Nikko)	16
PEG-20 monopalmitato de sorbitán	Tween-40 (Atlas/ICI), Crillet 2 (Croda)	16
PEG-20 monoestearato de sorbitán	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
PEG-4 monoestearato de sorbitán	Tween-61 (Atlas/ICI), Crillet 31 (Croda)	9,6
PEG-8 monoestearato de sorbitán	DACOL MSS (Condea)	>10
PEG-6 monoestearato de sorbitán	Nikkol TS 106 (Nikko)	11
PEG-20 triestearato de sorbitán	Tween-65 (Atlas/ICI), Crillet 35 (Croda)	11
PEG-6 tetraestearato de sorbitán	Nikkol GS-6 (Nikko)	3
PEG-60	Nikkol GS-460 (Nikko)	13

Ésteres de ácidos grasos de PEG-sorbitán		
Compuesto	**Producto comercial (proveedor)**	**EHL**
tetraestearato de sorbitán		
PEG-5 monooleato de sorbitán	Tween-81 (Atlas/ICI), Crillet 41 (Croda)	10
PEG-6 monooleato de sorbitán	Nikkol TO-106 (Nikko)	10
PEG-20 monooleato de sorbitán	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15
PEG-40 oleato de sorbitán	Emalex ET 8040, (Nihon Emulsion)	18
PEG-20 trioleato de sorbitán	Tween-85 (Atlas/ICI), Crillet 45 (Croda)	11
PEG-6 tetraoleato de sorbitán	Nikkol GO-4 (Nikko)	8,5
PEG-30 tetraoleato de sorbitán	Nikkol GO-430 (Nikko)	12
PEG-40 tetraoleato de sorbitán	Nikkol GO-440 (Nikko)	13
PEG-20 monoisostearato de sorbitán	Tween-120 (Atlas/ICI), Crillet 6 (Croda)	>10
PEG hexaoleato de sorbitol	Atlas G-1086 (ICI)	10
PEG-6 hexastearato de sorbitol	Nikkol GS-6 (Nikko)	3

TABLA 92

Éteres alquílicos de polietilenglicol

Los éteres de polietilenglicol y alquilalcoholes son tensioactivos adecuados para usar en la presente invención. En la tabla 92 se muestran ejemplos de estos tensioactivos.

Éteres alquílicos de polietilenglicol		
Compuesto	**Producto comercial (proveedor)**	**EHL**
PEG-2 oleil éter, oleth-2	Brij 92/93 (Atlas/ICI)	4,9
PEG-3 oleil éter, oleth-3	Volpo 3 (Croda)	<10
PEG-5 oleil éter, oleth-5	Volpo 5 (Croda)	<10
PEG-10 oleil éter, oleth-10	Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleil éter, oleth-20	Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauril éter, laureth-4	Brij 30 (Atlas/ICI)	9,7
PEG-9 lauril éter		>10
PEG-23 lauril éter, laureth-23	Brij 35 (Atlas/ICI)	17
PEG-2 cetil éter	Brij 52 (ICI)	5,3
PEG-10 cetil éter	Brij 56 (ICI)	13
PEG-20 cetil éter	Brij 58 (ICI)	16
PEG-2 estearil éter	Brij 72 (ICI)	4,9
PEG-10 estearil éter	Brij 76 (ICI)	12
PEG-20 estearil éter	Brij 78 (ICI)	15
PEG-100 estearil éter	Brij 700 (ICI)	>10

TABLA 93

Ésteres de azúcares

Los ésteres de azúcares son tensioactivos adecuados para usar en la presente invención. En la tabla 93 se muestran ejemplos de dichos tensioactivos.

Tensioactivos de ésteres de azúcares		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Diestearato de sacarosa	SUCRO ESTER 7 (Gattefosse), Crodesta F-10 (Croda)	3
Diestearato/ monoestearato de sacarosa	SUCRO ESTER 11 (Gattefosse), Crodesta F-110 (Croda)	12
Dipalmitato de sacarosa		7,4
Monoestearato de sacarosa	Crodesta F-160 (Croda)	15
Monopalmitato de sacarosa	SUCRO ESTER 15 (Gattefosse)	>10
Monolaurato de sacarosa	Monolaurato de sacarosa 1695 (Mitsubishi-Kasei)	15

TABLA 94

Polietilenglicol alquil fenoles

Se dispone de varios tensioactivos hidrófilos PEG-alquil fenol que son adecuados para usar en la presente invención. En la tabla 94 se muestran ejemplos de estos tensioactivos.

Tensioactivos polietilenglicol alquil fenoles		
Compuesto	**Producto comercial (proveedor)**	**EHL**
PEG-10-100 nonilfenol	Serie Triton X (Rohm & Haas), Serie Igepal CA (GAF, EE.UU), Serie Antarox CA (GAF, Reino Unido)	>10
PEG-15-100 octilfenol éter	Serie Triton N (Rohm & Haas), Serie Igepal CO (GAF, EE.UU), Serie Antarox CO (GAF, Reino Unido)	>10

TABLA 95

Copolímeros en bloque polioxietileno-polioxipropileno

Los copolímeros en bloque de OPE-OPP son una clase única de tensioactivos poliméricos. La estructura única 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 comercializan con diversos nombres comerciales, incluidos la serie Synperonic™ PE (ICI); la serie Pluronic® (BASF), Emkalyx™, Lutrol™ (BASF), Supronic™, Monolan™, Pluracare™ y Plurodac™. El término genérico para estos polímeros es "poloxámero" (CAS 9003-11-6). Estos polímeros tienen la fórmula:

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

donde "a" y "b" indican el número de unidades de polioxietileno y de polioxipropileno, respectivamente.

En la tabla 95 se muestran ejemplos de tensioactivos adecuados de esta clase. Puesto que los compuestos están ampliamente disponibles en el comercio no se indican en la Tabla las fuentes comerciales. Los compuestos se listan por su nombre genérico, con los correspondientes valores "a" y "b".

Copolímeros en bloque OPE-OPP			
Compuesto	**valores a,b en $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$**		**EHL**
Poloxámero 105	a = 11	b = 16	8
Poloxámero 108	a = 46	b = 16	>10
Poloxámero 122	a = 5	b = 21	3
Poloxámero 123	a = 7	b = 21	7
Poloxámero 124	a = 11	b = 21	>7
Poloxámero 181	a = 3	b = 30	
Poloxámero 182	a = 8	b = 30	2
Poloxámero 183	a = 10	b = 30	
Poloxámero 184	a = 13	b = 30	
Poloxámero 185	a = 19	b = 30	
Poloxámero 188	a = 75	b = 30	29
Poloxámero 212	a = 8	b = 35	
Poloxámero 215	a = 24	b = 35	
Poloxámero 217	a = 52	b = 35	
Poloxámero 231	a = 16	b = 39	

Copolímeros en bloque OPE-OPP			
Compuesto	**valores a,b en $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$**		**EHL**
Poloxámero 234	a = 22	b = 39	
Poloxámero 235	a = 27	b = 39	
Poloxámero 237	a = 62	b = 39	24
Poloxámero 238	a = 97	b = 39	
Poloxámero 282	a = 10	b = 47	
Poloxámero 284	a = 21	b = 47	
Poloxámero 288	a = 122	b = 47	>10
Poloxámero 331	a = 7	b = 54	0,5
Poloxámero 333	a = 20	b = 54	
Poloxámero 334	a = 31	b = 54	
Poloxámero 335	a = 38	b = 54	
Poloxámero 338	a = 128	b = 54	
Poloxámero 401	a = 6	b = 67	
Poloxámero 402	a = 13	b = 67	
Poloxámero 403	a = 21	b = 67	
Poloxámero 407	a = 98	b = 67	

TABLA 96

Ésteres de ácidos grasos de sorbitán

Los ésteres de ácidos grasos de sorbitán son tensioactivos adecuados para usar en la presente invención. En la tabla 96 se muestran ejemplos de estos tensioactivos.

Tensioactivos ésteres de ácidos grasos de sorbitán		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Monolaurato de sorbitán	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8,6
Monopalmitato de sorbitán	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6,7
Monooleato de sorbitán	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4,3
Monoestearato de sorbitán	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4,7
Trioleato de sorbitán	Span-85 (Atlas/ICI), Crill 45 (Croda), Nikkol SO-30 (Nikko)	4,3
Sesquioleato de sorbitán	Arlacel-C (ICI), Crill 43 (Croda), Nikkol SO-15 (Nikko)	3,7
Triestearato de sorbitán	Span-65 (Atlas/ICI) Crill 35 (Croda), Nikkol SS-30 (Nikko)	2,1
Monoisostearato de sorbitán	Crill 6 (Croda), Nikkol SI-10 (Nikko)	4,7
Sesquiestearato de sorbitán	Nikkol SS-15 (Nikko)	4,2

TABLA 97

Ésteres de ácidos grasos de alcoholes inferiores

Los ésteres de alcoholes inferiores (C_2 a C_4) y ácidos grasos (C_8 a C_{18}) son tensioactivos adecuados para usar en la presente invención. En la tabla 97 se muestran ejemplos de estos tensioactivos.

Tensioactivos ésteres de ácidos grasos de alcoholes inferiores		
Compuesto	**Producto comercial (proveedor)**	**EHL**
Oleato de etilo	Crodamol EO (Croda), Nikkol EOO (Nikko)	<10
Miristato de isopropilo	Crodamol IPM (Croda)	<10
Palmitato de isopropilo	Crodamol IPP (Croda)	<10
Linoleato de etilo	Nikkol VF-E (Nikko)	<10
Linoleato de isopropilo	Nikkol VF-IP (Nikko)	<10

TABLA 98

Tensioactivos iónicos

Los tensioactivos iónicos, incluidos los tensioactivos catiónicos, aniónicos y zwiteriónicos, son tensioactivos hidrófilos adecuados para usar en la presente invención. Los tensioactivos aniónicos preferidos incluyen sales de ácidos grasos y sales biliares. Los tensioactivos catiónicos preferidos incluyen carnitinas. Específicamente, los tensioactivos iónicos preferidos 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 carnitina y miristoil carnitina. Los ejemplos de dichos tensioactivos se muestran en la Tabla 98. Por simplicidad, se muestran los contraiones típicos en las entradas de la tabla. Los técnicos con experiencia en el área apreciarán, no obstante, que se puede usar cualquier contraión biológicamente aceptable. Por ejemplo, aunque los ácidos grasos se muestran como sales de sodio, se pueden usar también otros contraiones catiónicos, como cationes de metales alcalinos o amonio. A diferencia de los tensioactivos no iónicos típicos, estos tensioactivos iónicos están disponibles generalmente como compuestos puros en vez de mezclas (de marca registrada). Debido a que estos compuestos se pueden adquirir fácilmente de diversos proveedores comerciales, como Aldrich, Sigma y otros, en general no se indican en la tabla las fuentes comerciales.

Tensioactivos iónicos	
Compuesto	**EHL**
SALES DE ÁCIDOS GRASOS	>10
Caproato de sodio	
Caprilato de sodio	
Caprato de sodio	
Laurato de sodio	
Miristato de sodio	
Miristolato de sodio	
Palmitato de sodio	
Palmitoleato de sodio	
Oleato de sodio	18
Ricinoleato de sodio	
Linoleato de sodio	

Tensioactivos iónicos	
Compuesto	**EHL**
Linolenato de sodio	
Estearato de sodio	
Lauril sulfato de sodio (dodecil)	40
Tetradecil sulfato de sodio	
Lauril sarcosinato de sodio	
Dioctil sulfosuccinato de sodio [docusato de sodio (Cytec)]	
SALES BILIARES	>10
Colato de sodio	
Taurocolato de sodio	
Glicolato de sodio	
Desoxicolato de sodio	
Taurodesoxicolato de sodio	
Glicodesoxicolato de sodio	
Ursodesoxicolato de sodio	
Quenodesoxicolato de sodio	
Tauroquenodesoxicolato de sodio	
Glicol quenodesoxicolato de sodio	
Colilsarcosinato de sodio	
N-metil taurocolato de sodio	
Litocolato de sodio	
FOSFOLÍPIDOS	
Huevo/lecitina de soja [Epikuron™ (Lucas Meyer), Ovothin™ (Lucas Meyer)]	
Liso huevo/lecitina de soja	
Lecitina hidroxilada	
Lisofosfatidilcolina	
Cardiolipina	
Esfingomielina	
Fosfatidilcolina	
Fosfatidil etanolamina	
Ácido fosfatídico	
Fosfatidil glicerol	
Fosfatidil serina	
ÉSTERES DE ÁCIDO FOSFÓRICO	
Polioxietilen-10 oleil éter fosfato de dietanolamonio	
Productos de esterificación de alcoholes grasos o alcoholes grasos etoxilados con	

Tensioactivos iónicos	
Compuesto	**EHL**
ácido o anhídrido fosfórico	
CARBOXILATOS	
Éter carboxilatos (por oxidación del grupo OH terminal de etoxilatos de alcoholes grasos)	
Monoglicéridos succinilados [LAMEGIN ZE (Henkel)]	
Estearil fumarato de sodio	
Propilenglicol hidrógeno succinato de estearoilo	
Ésteres de ácido tartárico mono/diacetilados de mono/diglicéridos	
Ésteres de mono y diglicéridos del ácido cítrico	
Gliceril-lacto ésteres de ácidos grasos (CFR ref. 172.852)	
Acil lactilatos: ésteres lactílicos de ácidos grasos de calcio/sodio estearoil-2-lactilato calcio/estearoil lactilato de sodio	
Sales de alginatos	
Alginato de propilenglicol	
SULFATOS Y SULFONATOS	
Alquil sulfatos etoxilados	
Alquil benceno sulfonas	
α-olefin sulfonatos	
Isetionatos de acilo	
Tauratos de acilo	
Alquil gliceril éter sulfonatos	
Octil sulfosuccinato disódico	
Undecilenamido-MEA-sulfosuccinato disódico	
Tensioactivos CATIÓNICOS	>10
Lauroil carnitina	
Palmitoil carnitina	
Miristoil carnitina	
Bromuro de hexadecil triamonio	
Bromuro de decil trimetil amonio	
Bromuro de cetil trimetil amonio	
Cloruro de dodecil amonio	
Sales de alquil bencildimetilamonio	

Tensioactivos iónicos	
Compuesto	**EHL**
Sales de diisobutil fenoxietoxidimetil bencilamonio	
Sales de alquilpiridinio	
Betaínas (trialquilglicina):	
Lauril betaína (N-lauril,N,N-dimetilglicina)	
Aminas etoxiladas:	
Polioxietileno-15 cocoamina	

Tabla 99

COMPRIMIDOS DE BUPROPION HBr XL de 348 mg
COMPOSICIÓN DE LOS COMPRIMIDOS (mg/comprimido)

Tabla 1 Núcleo de los comprimidos

N° de artículo	Material	Cant. necesaria (kg)	% del comprimido de la formulación del núcleo del comprimido	348 mg de dosis Peso de referencia: 371,2 mg/comprimido
RS0009	Alcohol polivinílico	2,25 kg dispensados 2,00 kg usados	3,125 %	11,6 mg/comprimido
RA0057	Bupropion HBr	60,00	93,750 %	348 mg/comprimido
RE0200	Behenato de glicerilo, NF	2,00	3,125 %	11,6 mg/comprimido
RS0003	*Agua purificada, USP	47,75	0	0
Tamaño teórico del lote: kg		64,00	100 %	371,2 mg/comprimido

*Evaporada durante el proceso de granulación y no incluida en la composición del núcleo del comprimido.

TABLA 100

Tabla 2: Comprimidos recubiertos/impresos

Comprimidos XL recubiertos de 348 mg - Formulación de recubrimiento fundamental / Tamaño del lote				
N° de artículo	Material	Cant. necesaria (kg)	% del lote	Sólidos aplicados mg/comprimido Aumento de peso de referencia 32 mg (Intervalo: 30-34 mg/comprimido)
RE0233	Etilcelulosa 100, NF	3,230	4,61 %	16,406 mg
RE0067	Povidona, USP	2,000	2,86 %	10,159 mg
RE0331	Polietilenglicol 4000, NF	0,720	1,03 %	3,657 mg
RE0103	Sebacato de dibutilo, NF	0,350	0,50 %	1,778 mg
*RS0010	*Alcohol deshidratado, 200 de graduación, USP	57,300	81,86 %	0
*RS0006	*Alcohol etílico, 95 % USP	6,400	9,14 %	0
TOTAL DE SOLUCIÓN DE RECUBRIMIENTO (kg)		70 kg	100 %	32 mg/comprimido
**RE0223	**Cera carnauba, NF	0,010 kg	N/A	Cantidades traza
RE0234	Tinta negra Opacode S-1-8090 o S-1-17823	1,00	50 %	Cantidades traza para marcar los comprimidos con el logotipo sobre un lado BR 348

TOTAL DE SOLUCIÓN DE RECUBRIMIENTO (kg)		70 kg	100 %	32 mg/comprimido
***RS0001	***Alcohol isopropílico	1,00	50 %	Usado sólo para la limpieza de los rodillos de diseño y transferencia

Nota: En los casos en que fue pertinente, los porcentajes y los totales de mg/comprimido se redondearon a dos cifras decimales. *Evaporada durante el proceso de recubrimiento. **La cera carnauba no se incluyó como parte de la formulación de la solución de recubrimiento, se aplicaron trazas después de completar el proceso de recubrimiento. ***El alcohol isopropílico se usó sólo para limpieza. Sólo se aplican trazas de tinta negra para marcar los comprimidos con el logotipo específico en un lado del comprimido. El peso de este material aplicado al comprimido no se puede medir.

TABLA 101

Tabla 3: COMPRIMIDOS DE BUPROPION HBr XL de 348 mg: COMPOSICIÓN GENERAL DEL COMPRIMIDO IMPRESO FINAL/PESO

Material	**348 mg** (+32 mg Recubrimiento)/ % general de la composición del comprimido final
Alcohol polivinílico	11,6 mg (2,88 %)
Bupropion HBr (IFA)	348 mg (86,29 %)
Agua purificada, USP	0
Behenato de glicerilo, NF	11,6 mg (2,88 %)
Etilcelulosa 100, NF	16,406 mg (4,07 %)
Povidona, USP	10,159 mg (2,52 %)
Polietilenglicol 4000, NF	3,657 mg (0,91 %)
Sebacato de dibutilo, NF	1,778 mg (0,44 %)
Alcohol deshidratado, 200 de graduación, USP	0
Alcohol etílico, 95 % USP	0
Cera carnauba, NF	0,058 mg/comprimido (0,01 %) (basado en una carga de la paila para recubrimiento de 172.413 comprimidos)
Tinta negra Opacode S-1-8090 o S-1-17823	Cantidades traza
Alcohol isopropílico	0
Peso del comprimido impreso final (mg)	403,258 mg/comprimido (100 %)

NOTA: Los comprimidos de Bupropion HBr XL de 174 mg y 348 mg tienen la misma formulación de núcleo del comprimido y de recubrimiento (composición). La única diferencia en el porcentaje del material por comprimido se debe a las diferencias en el peso del núcleo del comprimido y del aumento de peso del recubrimiento. La cantidad total de cera carnauba aplicada a los comprimidos variará basada en la carga de la paila de recubrimiento. La composición porcentual (%) de cada ingrediente en la formulación del

comprimido final, se basa para los cálculos en el aumento de peso de referencia del recubrimiento final y la cantidad de referencia de cera carnauba.

TABLA 102

COMPRIMIDOS DE BUPROPION HBr XL de 174 mg
COMPOSICIÓN DE LOS COMPRIMIDOS (mg/comprimido)

Tabla 1: Núcleos de los comprimidos

N° de artículo	**Material**	**Cant. necesaria (kg)**	**% del comprimido de la formulación del núcleo del comprimido**	**174 mg de dosis Peso de referencia: 185,6 mg/comprimido**
RS0009	Alcohol polivinílico	2,25 kg dispensados / 2,00 kg usados	3,125 %	5,8 mg/comprimido
RA0057	Bupropion HBr	60,00	93,750 %	174 mg/comprimido
RE0200	Behenato de glicerilo, NF	2,00	3,125 %	5,8 mg/comprimido
RS0003	*Agua purificada USP	47,75	0	0
Tamaño teórico del lote: kg		64,00	100 %	185,6 mg/comprimido

*Evaporada durante el proceso de granulación y no incluida en la composición del núcleo del comprimido.

TABLA 103

Tabla 2: Comprimidos recubiertos/impresos

Comprimidos XL recubiertos/impresos de 174 mg - Formulación de recubrimiento fundamental / Tamaño del lote				
N° de artículo	**Material**	**Cant. necesaria (kg)**	**% del lote**	**Sólidos aplicados mg/comprimido** **Aumento de peso de referencia: 30 mg (Intervalo: 28-32 mg/comprimido)**
RE0233	Etilcelulosa 100, NF	3,230	4,61 %	15,381 mg
RE0067	Povidona, USP	2,000	2,86 %	9,524 mg
RE0331	Polietilenglicol 4000, NF	0,720	1,03 %	3,428 mg
RE0103	Sebacato de dibutilo, NF	0,350	0,50 %	1,667 mg
*RS0010	*Alcohol deshidratado, 200 de graduación, USP	57,300	81,86 %	0
*RS0006	*Alcohol etílico, 95 % USP	6,400	9,14 %	0
TOTAL DE SOLUCIÓN DE RECUBRIMIENTO (kg)		70 kg	100 %	30 mg/comprimido
**RE0223	**Cera carnauba, NF	0,010 kg	N/A	Cantidades traza
RE0234	Tinta negra Opacode S-1-8090 o S-1-17023	1,00	50 %	Cantidades traza para marcar los comprimidos con el logotipo sobre un lado BR 174
***RS0001	***Alcohol isopropílico	1,00	50 %	Usado sólo para la limpieza de los rodillos de diseño y transferencia

Nota: En los casos en que fue pertinente, los porcentajes y los totales de mg/comprimido se redondearon a dos cifras decimales. *Evaporada durante el proceso de recubrimiento. **La cera carnauba no se incluyó como parte de la formulación de la solución de recubrimiento,

se aplicaron trazas después de completar el proceso de recubrimiento. ***El alcohol isopropílico se usó sólo para limpieza. Sólo se aplican trazas de tinta negra para marcar los comprimidos con el logotipo específico en un lado del comprimido. El peso de este material aplicado al comprimido no se puede medir.

TABLA 104

Tabla 3: COMPRIMIDOS DE BUPROPION HBr XL de 174 mg: COMPOSICIÓN GENERAL DEL COMPRIMIDO IMPRESO FINAL/PESO

Material	**174 mg (+30 mg Recubrimiento)/ % general de la composición del comprimido final**
Alcohol polivinílico	5,8 mg (2,69 %)
Bupropion HBr (IFA)	174 mg (80,68 %)
Agua purificada, USP	0
Behenato de glicerilo, NF	5,8 mg (2,69 %)
Etilcelulosa 100, NF	15,381 mg (7,13 %)
Povidona, USP	9,524 mg (4,42 %)
Polietilenglicol 4000, NF	3,428 mg (1,59 %)
Sebacato de dibutilo, NF	1,667 mg (0,77 %)
Alcohol deshidratado, 200 de graduación, USP	0
Alcohol etílico, 95 % USP	0
Cera carnauba, NF	0,058 mg/comprimido (0,03%) (basado en una carga de la paila para recubrimiento de 172.413 comprimidos)
Tinta negra Opacode S-1-8090 o S-1-17823	Cantidades traza
Alcohol isopropílico	0
Peso del comprimido impreso final (mg)	215,658 mg/comprimido (100 %)

NOTA: Los comprimidos de Bupropion HBr XL de 174 mg y 348 mg tienen la misma formulación de núcleo del comprimido y de recubrimiento (composición). La única diferencia en el porcentaje del material por comprimido se debe a las diferencias en el peso del núcleo del comprimido y del aumento de peso del comprimido. La cantidad total de cera carnauba aplicada a los comprimidos variará basada en la carga de la paila de recubrimiento. La composición porcentual (%) de cada ingrediente en la formulación del comprimido final, se basa para los cálculos en el aumento

de peso de referencia del recubrimiento final y la cantidad de referencia de cera carnauba.

TABLA 105(1)

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL				
Producto: Bupropion HBr FV0092	N° de lote: D00894	Fecha de inicio: 20/12/04		Temperatura: 40°C ± 2°C H.R.: 75 % ± 5 %
Análisis	Especificación	tiempo 0	3 meses	6 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva
Contenido de agua (K.F.)	NMD 0,5 %	0,05	0,07	0,08
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,06	4) 0,04 5) n.c. 6) 0,02
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,6	99,6	99,7

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

Datos de estabilidad de bupropion HBr

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TABLA 105(2)

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL				
Producto: Bupropion HBr FV0092	N° de lote: D00895	Fecha de inicio: 20/12/04	Temperatura: 40°C ± 2°C H.R.: 75 % ± 5 %	
Análisis	Especificación	tiempo 0	3 meses	6 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva
Contenido de agua (K.F.)	NMD 0,5 %	0,04	0,07	0,07
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) 0,05	1) 0,05 2) n.d. 3) n.c.
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,05	4) 0,04 5) n.c. 6) 0,02
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,2	100,7	99,7
Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC). Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.				

Datos de estabilidad de bupropion HBr

TABLA 105(3)

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL				
Producto: Bupropion HBr FV0092	N° de lote: D00896	Fecha de inicio: 20/12/04	Temperatura: 40°C ± 2°C H.R.: 75 % ± 5 %	
Análisis	Especificación	tiempo 0	3 meses	6 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva
Contenido de agua (K.F.)	NMD 0,5 %	0,06	0,11	0,04
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,05 6) 0,05	4) 0,03 5) 0,04 6) 0,05	4) 0,04 5) n.c. 6) n.c.
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,3	100,0	100,4

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

Datos de estabilidad de bupropion HBr

TABLA 105(4)

VIDA ÚTIL

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL									
Producto: Bupropion HBr FV0092	N° de lote: D00894			Fecha de inicio: 20/12/04			Temperatura: 25° C ± 2° C Humedad relativa: 60 % ± 5 %		
Análisis	Especificación	tiempo 0	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple	cumple	cumple			
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva	positiva	positiva			
Contenido de agua (K.F.)	NMD 0,5 %	0,05	0,05	0,06	0,05	0,05			
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) n.d. 2) n.d. 3) 0,05	1) 2) 3)	1) 2) 3)	1) 2) 3)
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,05	4) 0,05 5) n.c. 6) 0,02	4) n.d. 5) n.c. 6) n.c.	4) 0,05 5) 0,05 6) 0,07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1	n.c.	0,2			
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,6	99,4	100,2	99,5	99,6			
Contenido microbiológico	• recuento microbiológico total < 1000 ufc/g • hongos y levaduras < 100 ufc/g	no se aplicó	no se aplicó	no se aplicó	no se aplicó	< 100 ufc/g < 100 ufc/g	no se aplicó		

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

Datos de estabilidad de bupropion HBr

TABLA 105(5)

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL									
Producto: Bupropion HBr FV0092	N° de lote: D00895			Fecha de inicio: 20/12/04			Temperatura: 25° C ± 2° C Humedad relativa: 60 % ± 5 %		
Análisis	Especificación	tiempo 0	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple	cumple	cumple			
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva	positiva	positiva			
Contenido de agua (K.F.)	NMD 0,5 %	0,04	0,04	0,05	0,05	0,04			
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) n.d. 2) n.d. 3) 0,05	1) 2) 3)	1) 2) 3)	1) 2) 3)
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,04 6) 0,04	4) 0,03 5) 0,04 6) 0,05	4) 0,05 5) n.c. 6) 0,02	4) n.d. 5) n.c. 6) n.c.	4) 0,05 5) 0,07 6) 0,07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1	n.c.	0,2			
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,2	99,5	100,1	99,4	99,4			
Contenido microbiológico	• recuento microbiológico total < 1000 ufc/g • hongos y levaduras < 100 ufc/g	no se aplicó	no se aplicó	no se aplicó	no se aplicó	< 100 ufc/g < 100 ufc/g	no se aplicó		

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

Datos de estabilidad de bupropion HBr

TABLA 105(6)

PROGRAMA DE ESTABILIDAD DE VIDA ÚTIL									
Producto: Bupropion HBr FV0092	N° de lote: D00896		Fecha de inicio: 20/12/04			Temperatura: 25° C ± 2° C Humedad relativa: 60 % ± 5 %			
Análisis	Especificación	tiempo 0	3 meses	6 meses	9 meses	12 meses	18 meses	24 meses	36 meses
Descripción	polvo cristalino blanco o casi blanco	cumple	cumple	cumple	cumple	cumple			
Identificación	IR, HPLC (positiva)	positiva	positiva	positiva	positiva	positiva			
Contenido de agua (K.F.)	NMD 0,5 %	0,06	0,04	0,04	0,04	0,03			
Pureza cromatográfica A) (HPLC)	1) NMD 0,1 % 2) NMD 0,1 % 3) NMD 0,1 %	1) n.d. 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) 0,05 2) n.d. 3) n.c.	1) n.c. 2) n.d. 3) n.c.	1) n.d. 2) n.d. 3) n.c.	1) 2) 3)	1) 2) 3)	1) 2) 3)
Pureza cromatográfica B) (HPLC)	4) NMD 0,1 % 5) NMD 0,1 % 6) NMD 0,3 %	4) 0,04 5) 0,05 6) 0,05	4) 0,03 5) 0,04 6) 0,05	4) 0,04 5) n.c. 6) n.c.	4) n.d. 5) n.c. 6) n.c.	4) 0,05 5) 0,07 6) 0,07	4) 5) 6)	4) 5) 6)	4) 5) 6)
Pureza cromatográfica (HPLC: A + B)	Impurezas totales NMD 0,5 %	0,1	0,1	0,1	n.c	0,1			
Contenido (HPLC)	98,0 - 102,0 % en la base de datos	99,3	99,4	100,5	99,4	100,3			
Contenido microbiológico	• recuento microbiológico total < 1000 ufc/g • hongos y levaduras < 100 ufc/g	no se aplicó	no se aplicó	no se aplicó	no se aplicó	< 100 ufc/g < 100 ufc/g	no se aplicó		

Impurezas: 1) 3'-Cloropropiofenona; 2) 3'-Cloro-2-bromopropiofenona; 3) Ácido 3'-clorobenzoico; 4) 2-N-(tercbutil)-aminopropiofenona; 5) impurezas desconocidas (cada una); 6) impurezas desconocidas totales (calculadas a partir de la suma del área de todos los picos de impurezas, también se incluyen picos por debajo del LDC).
Notas: n.d. = no detectable; n.c. = no cuantificable; LDC (límite de cuantificación) = 0,05 % para imp. 1, 2 y 3; LDC = 0,02 % para imp. 4 y 5; LDD (límite de decisión) = 0,01 % para imp. 1 y 3; LDD = 0,04 % para imp. 2; LDD = 0,002 % para imp. 4 y 5.

Datos de estabilidad de bupropion HBr

REIVINDICAMOS:

1. Una composición adecuada para la administración a un sujeto que necesita tratamiento para una afección, que comprende:

una cantidad farmacéuticamente eficaz de sal bromhidrato de bupropion,

donde dicha composición de bromhidrato de bupropion es más estable que una composición correspondiente que comprende clorhidrato de bupropion.

2. La composición de la reivindicación 1 donde dicha composición es adecuada para la administración oral a un sujeto que necesita la administración de bupropion.

3. La composición de la reivindicación 1 donde dicha composición de bromhidrato de bupropion es más estable que una composición, por lo demás equivalente, de clorhidrato de bupropion cuando se las almacena durante al menos 3 meses a 40 grados C y 75 % de humedad relativa.

4. La composición de la reivindicación 3 que es más estable cuando se la almacena durante al menos 6 meses a 40 grados C y 75 % de humedad relativa.

5. La composición de la reivindicación 3 que contiene menos de al menos un producto de degradación característico de la degradación de bupropion después de haber sido almacenada a 40 grados C a 75 % de humedad relativa que una composición, por lo demás similar, de clorhidrato de bupropion almacenada en las mismas condiciones.

6. La composición de la reivindicación 3 que presenta menos fluctuaciones en el perfil de la disolución in vitro en al menos un medio de disolución que otra composición, por lo demás equivalente, de

absorción rápida de la dosis cuando dicha composición está en etanol al 40 %.

8. La composición de la reivindicación 7 que comprende SmartCoat™.

9. La composición de la reivindicación 1 que comprende al menos un vehículo o excipiente farmacéuticamente aceptables.

10. La composición de la reivindicación 1 que está en la forma de un comprimido que es bioequivalente a los comprimidos de Wellbutrin™ o Zyban™/Wellbutrin™ SR cuando se administra una vez al día a un sujeto que la necesita.

11. La composición de la reivindicación 10 que no presenta un efecto por el consumo de alimentos.

12. La composición de la reivindicación 10 que comprende 150, 174, 300 ó 348 mg de clorhidrato de bupropion.

13. La composición de la reivindicación 1 que es adecuada para la administración por vía tópica.

14. La composición de la reivindicación 1 que es adecuada para la administración por vía transmucosa o transdérmica.

15. La composición de la reivindicación 1 que es adecuada para la administración por inyección.

16. La composición de la reivindicación 1 que es adecuada para la administración por inhalación.

17. La composición de la reivindicación 1 en la que el bupropion contenido comprende al menos 90 % de una forma enantiomérica de la sal de bupropion.

18. La composición de la reivindicación 1 en la que el bupropion contenido comprende al menos 95 % a 99 % de una forma enantiomérica de la sal de bupropion.

19. La composición de la reivindicación 1 en la que al menos 90 % del bupropion contenido comprende el enantiómero (+).

20. La composición de la reivindicación 1 en la que al menos 90 % del bupropion contenido comprende el enantiómero (-).

21. La composición de la reivindicación 1 en la que al menos 95 % a 99 % del bupropion comprende el enantiómero (-).

22. La composición de la reivindicación 1 en la que al menos 95 % a 99 % del bupropion comprende el enantiómero (+).

23. La composición de la reivindicación 1 que comprende al menos una de las formas polimórficas I, II y III.

24. La composición de la reivindicación 23 que comprende las formas polimórficas I, II y III.

25. Una forma polimórfica prácticamente pura de clorhidrato de bupropion.

26. El polimorfo prácticamente puro de la reivindicación 25 que es el polimorfo I.

27. El polimorfo prácticamente puro de la reivindicación 25 que es el polimorfo II.

28. El polimorfo prácticamente puro de la reivindicación 25 que es el polimorfo III.

29. La composición de la reivindicación 1 que es una formulación en comprimidos.

30. La composición de la reivindicación 1 que es una formulación en cápsulas.

31. La composición de la reivindicación 1 en la que dicha composición es una formulación de liberación extendida.

32. La composición de la reivindicación 1 en la que dicha composición es una formulación de liberación retarda.

33. La composición de la reivindicación 1 que es una formulación de absorción mejorada.

34. La composición de la reivindicación 1 que es una formulación en comprimidos de matriz de liberación controlada.

35. La composición de la reivindicación 1 que es un sistema de administración de liberación osmótica.

36. La composición de la reivindicación 1 que es adecuada para la administración una vez al día.

37. La composición de la reivindicación 1 que es adecuada para la administración dos veces al día.

38. La composición de la reivindicación 28 que es bioequivalente al Wellbutrin ER o Zyban™/Wellbutrin SR cuando se administra una vez al día.

39. La composición de la reivindicación 1 que comprende de 50 a 400 mg de bupropion.

40. La composición de la reivindicación 1 que comprende 150 ó 174 mg de bupropion.

41. La composición de la reivindicación 1 que comprende 300 ó 348 mg de bupropion.

42. La composición de la reivindicación 1 que comprende al menos un recubrimiento funcional o no funcional.

43. La composición de la reivindicación 42 en la que dichos recubrimientos incluyen barreras contra la humedad, recubrimientos con control de la liberación, recubrimientos entéricos, recubrimientos que afectan a la estabilidad física y/o recubrimientos que afectan al aspecto de la composición.

44. La composición de la reivindicación 43 que comprende una barrera contra la humedad.

45. La composición de la reivindicación 1 que comprende un núcleo que incluye dicha sal de bupropion, un aglutinante y un lubricante; y un recubrimiento de control de la liberación prácticamente rodeando dicho núcelo donde dicha composición proporciona liberación controlada de dicha sal de bupropion.

46. La composición de la reivindicación 45 que comprende al menos un recubrimiento adicional.

47. La composición de la reivindicación 45 en la que dichos recubrimientos adicionales incluyen barreras contra la humedad, recubrimientos entéricos, recubrimientos con control de la liberación, recubrimientos que afectan a la estabilidad física de la composición y/o recubrimientos que afectan al aspecto físico de la composición.

48. La composición de la reivindicación 47 en la que dichos recubrimientos adicionales prácticamente rodean el núcleo y/o el recubrimiento de control de la liberación.

49. La composición de la reivindicación 45 en la que dicho aglutinante es alcohol polivinílico.

50. La composición de la reivindicación 45 que comprende una barrera contra la humedad o un recubrimiento entérico rodeando el núcleo y/o el recubrimiento de control de la liberación.

51. La composición de la reivindicación 45 en la que dicho lubricante es behenato de glicerilo.

52. La composición de la reivindicación 45 en la que dicho recubrimiento de control de la liberación incluye un polímero insoluble en agua, un polímero soluble en agua y opcionalmente un plastificante.

53. La composición de la reivindicación 52 en la que dicho polímero insoluble en agua es etilcelulosa.

54. La composición de la reivindicación 52 en la que dicho polímero soluble en agua es polivinilpirrolidona.

55. La composición de la reivindicación 52 en la que dicho plastificante, si está presente, comprende una mezcla de polietilenglicol 4000 y sebacato de dibutilo.

56. La composición de la reivindicación 52 en la que dicho recubrimiento de control de la liberación incluye una dispersión acuosa de un copolímero de un éster neutro sin ningún grupo funcional, un poliglicol con un punto de fusión mayor de alrededor de 55°C y uno o más excipientes farmacéuticamente aceptables; donde dicho recubrimiento se aplica sobre dicho núcleo y se cura a una temperatura al menos igual o mayor que el punto de fusión del poliglicol.

57. La composición de la reivindicación 56 que comprende al menos un recubrimiento adicional.

58. La composición de la reivindicación 55 en la que dicho núcleo es una micropartícula.

59. La composición de la reivindicación 55 en la que dicho núcleo es un núcleo de liberación inmediata.

60. La composición de la reivindicación 1 que comprende además un segundo fármaco.

61. La composición de la reivindicación 60 en la que dicho segundo fármaco se selecciona entre un antidepresivo, un vasodilator, un ansiolítico, un antiinflamatorio, un analgésico, un antijaquecoso, un fármaco para combatir el abuso de drogas, alcohol o nicotina, un antiviral, un modulador del sueño, un antimimético, un anorexígeno o un estimulador del apetito y un fármaco neuropsiquiátrico.

62. La composición de la reivindicación 60 en la que el segundo fármaco es un antidepresivo.

63. La composición de la reivindicación 60 en la que el segundo fármaco se libera inmediatamente después de la administración.

64. La composición de la reivindicación 60 en la que el segundo fármaco no entra en contacto con el primer fármaco de la composición.

65. La composición de la reivindicación 64 en la que el bupropion y el segundo fármaco están comprendidos en capas, porciones de la composición o micropartículas diferentes que están comprendidas en la composición.

66. La composición de la reivindicación 60 en la que dicho segundo fármaco es citalopram.

67. La composición de la reivindicación 60 en la que dicho segundo fármaco es escitalopram.

68. La composición de la reivindicación 60 en la que el segundo fármaco es venlafaxina.

69. Un método para usar una composición de acuerdo con cualquiera de las reivindicaciones 1 a 68 para usar en el tratamiento de un sujeto que necesita la administración de bupropion.

70. El método de la reivindicación 69 donde dicha afección se selecciona del grupo que consiste en depresión, adicción, cesación del tabaquismo, obesidad y trastorno afectivo estacional.

71. El método de la reivindicación 69 donde dicha afección es obesidad.

72. El método de la reivindicación 69 donde la afección es obesidad.

73. El método de la reivindicación 69 donde la afección es cesación del hábito de fumar.

74. El método de la reivindicación 69 donde la afección es trastorno afectivo estacional.

75. El uso del bromhidrato de bupropion para preparar un medicamento para tratar las afecciones que se benefician de la administración de bupropion, donde dicho medicamento tiene mayor estabilidad que un medicamento correspondiente que comprenda clorhidrato de bupropion.

76. El uso de la reivindicación 75 donde dicha mayor estabilidad da como resultado dicho medicamento de bromhidrato de bupropion que contiene menos de al menos una porción característica de la degradación de bupropion que una composición, por lo demás similar, de clorhidrato de bupropion cuando ambas composiciones se almacenan durante al menos 3 meses o al menos 6 meses a 40 grados C y 75 % de humedad relativa.

77. El uso de la reivindicación 75 donde dicha mayor estabilidad da como resultado dicho medicamento de bromhidrato de bupropion que presenta menos fluctuaciones en el perfil de disolución in vitro en al menos un medio de disolución en relación con otra composición, por lo demás similar, de clorhidrato de bupropion después de haber sido almacenadas durante al menos 3 meses y/o 6 meses a 40 grados C y 75 % de humedad relativa.

78. El uso de la reivindicación 75 donde dicho medicamento es un comprimido.

79. El uso de la reivindicación 75 donde dicho medicamento es una cápsula.

80. El uso de la reivindicación 75 donde dicho medicamento contiene un segundo fármaco.

81. El uso de la reivindicación 80 donde el segundo fármaco es citalopram.

82. El uso de la reivindicación 80 donde el segundo fármaco es escitalopram.

83. El uso de la reivindicación 80 donde el segundo fármaco es venlafaxina.

FIGURA 1

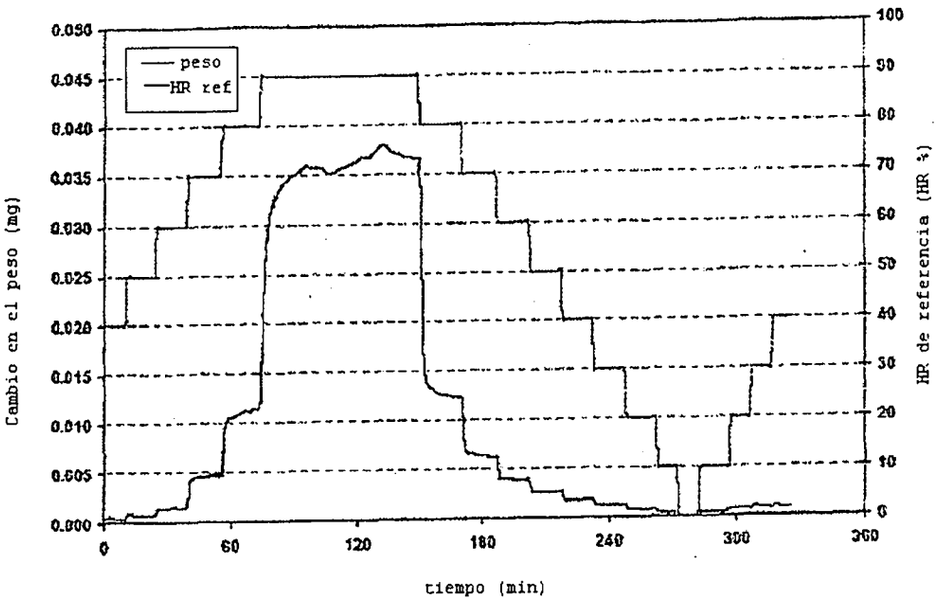

peso
HR ref
Cambio en el peso (mg)
HR de referencia (HR %)
tiempo (min)
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
100
90
80
70
60
50
40
30
20
10
0
0
60
120
180
240
300
360

FIGURA 2

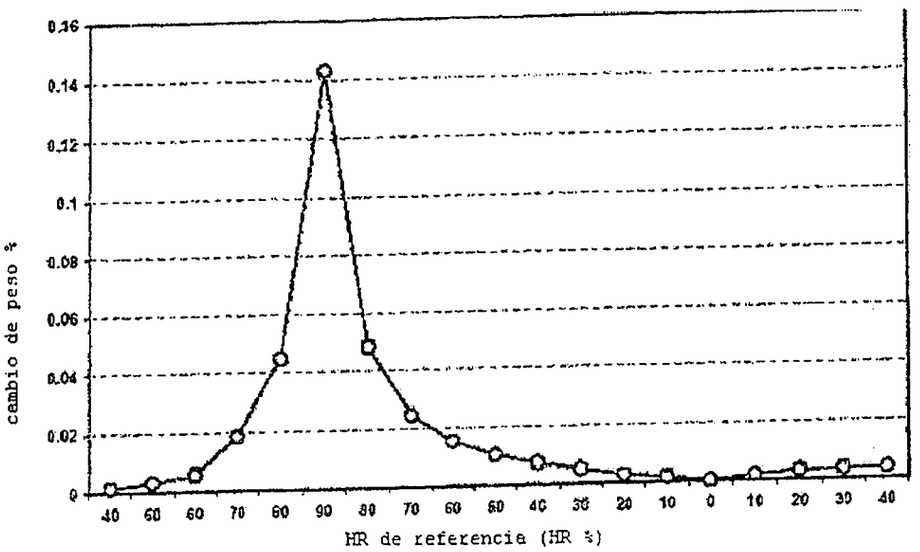

0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
cambio de peso %
40 50 60 70 80 90 80 70 60 50 40 30 20 10 0 10 20 30 40
HR de referencia (HR %)

FIGURA 3

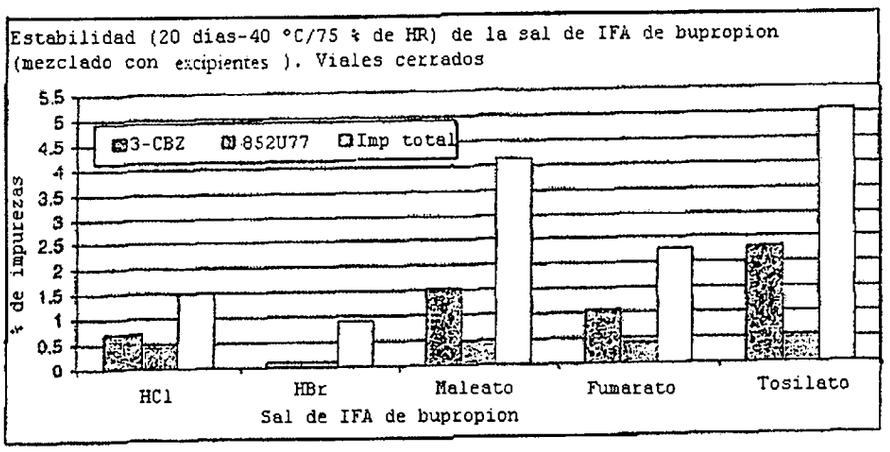

Estabilidad (20 días-40 °C/75 % de HR) de la sal de IFA de bupropion (mezclado con excipientes). Viales cerrados
3-CBZ
852U77
Imp total
% de impurezas
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
HCl
HBr
Maleato
Fumarato
Tosilato
Sal de IFA de bupropion

FIGURA 4

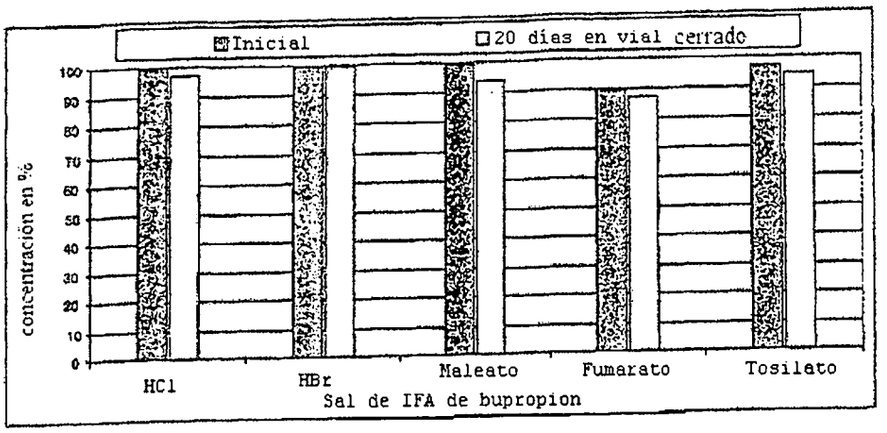

Inicial
20 días en vial cerrado
concentración en %
100
90
80
70
60
50
40
30
20
10
0
HCl
HBr
Maleato
Fumarato
Tosilato
Sal de IFA de bupropion

FIGURA 5

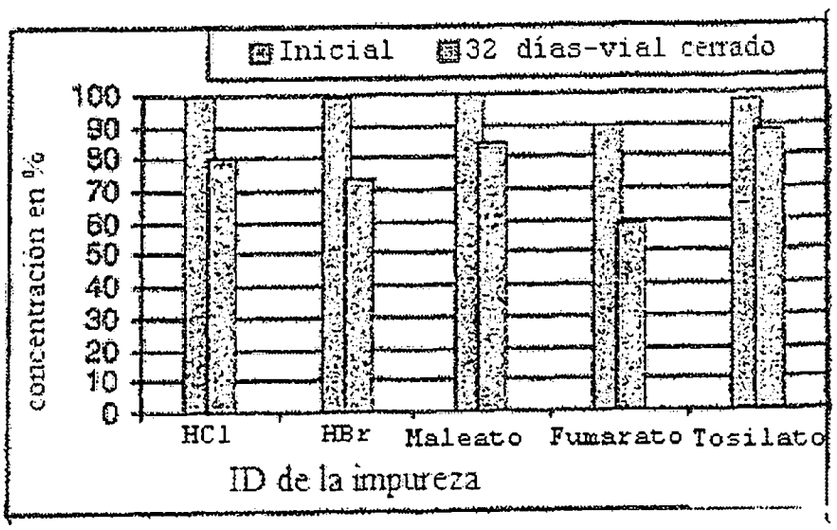

Inicial
32 días-vial cerrado
concentración en %
100
90
80
70
60
50
40
30
20
10
0
HCl
HBr
Maleato
Fumarato
Tosilato
ID de la impureza

FIGURA 6

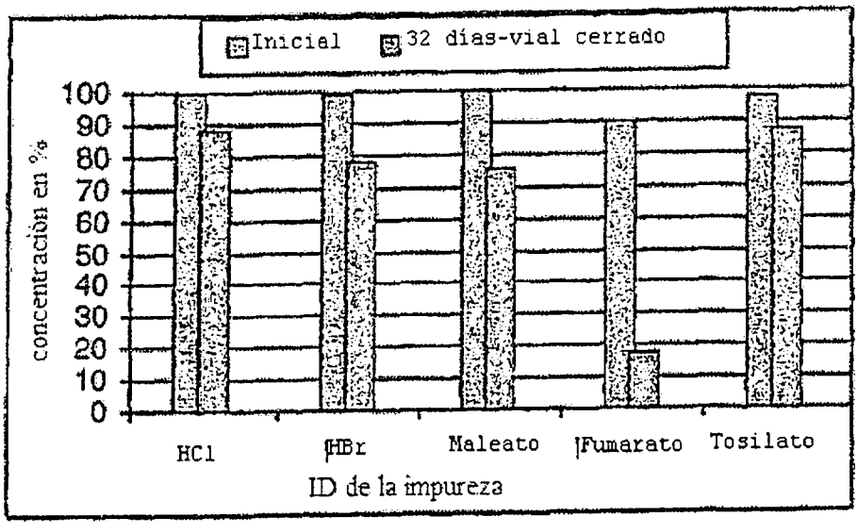

Inicial
32 días-vial cerrado
concentración en %
100
90
80
70
60
50
40
30
20
10
0
HCl
HBr
Maleato
Fumarato
Tosilato
ID de la impureza

FIGURA 7

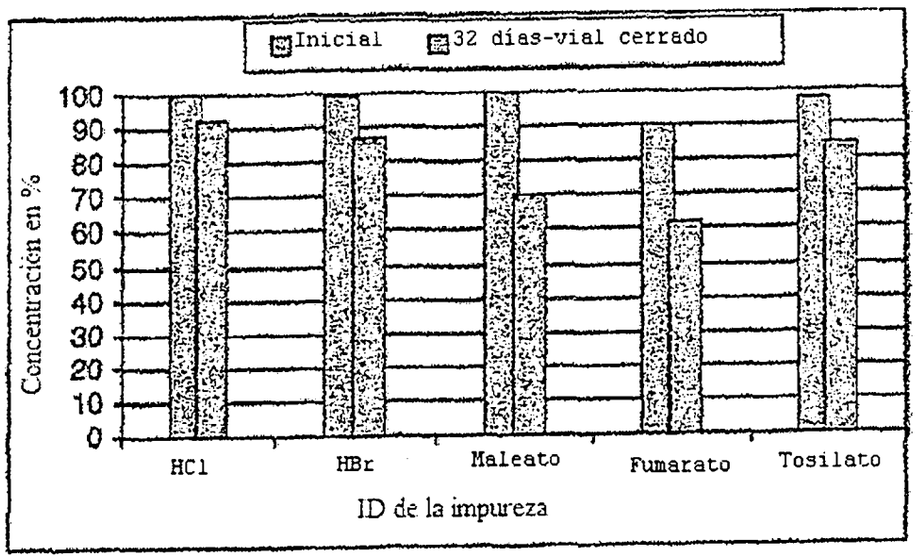
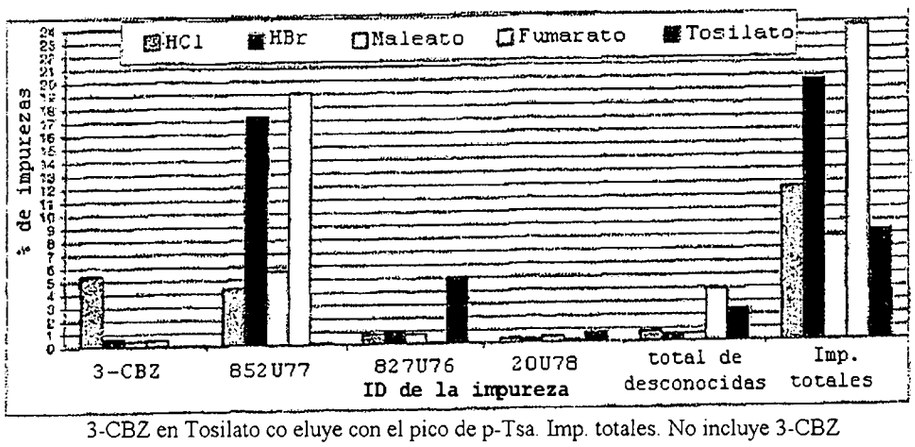
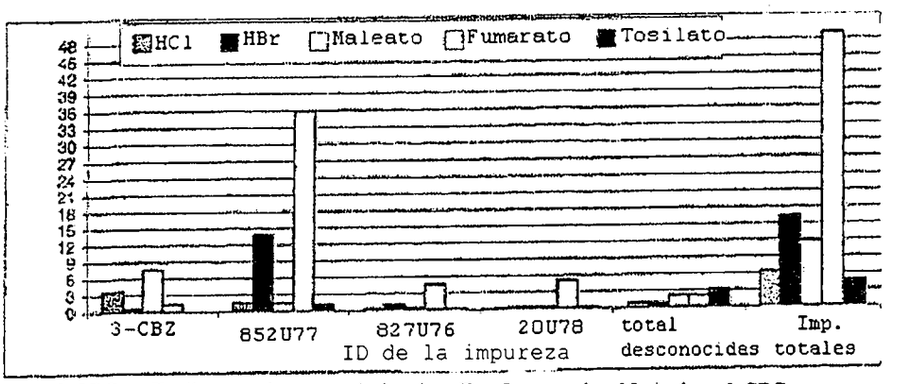

Inicial
32 días-vial cerrado
Concentración en %
100
90
80
70
60
50
40
30
20
10
0
HCl
HBr
Maleato
Fumarato
Tosilato
ID de la impureza

FIGURA 8



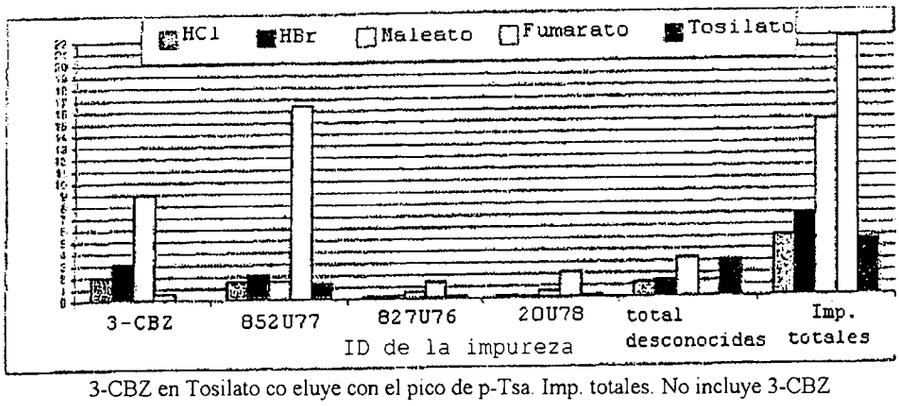
3-CBZ en Tosilato co eluye con el pico de p-Tsa. Imp. totales. No incluye 3-CBZ

FIGURA 9



3-CBZ en Tosilato co eluye con el pico de p-Tsa. Imp. totales. No incluye 3-CBZ

FIGURA 10



3-CBZ en Tosilato co eluye con el pico de p-Tsa. Imp. totales. No incluye 3-CBZ

FIGURA 11

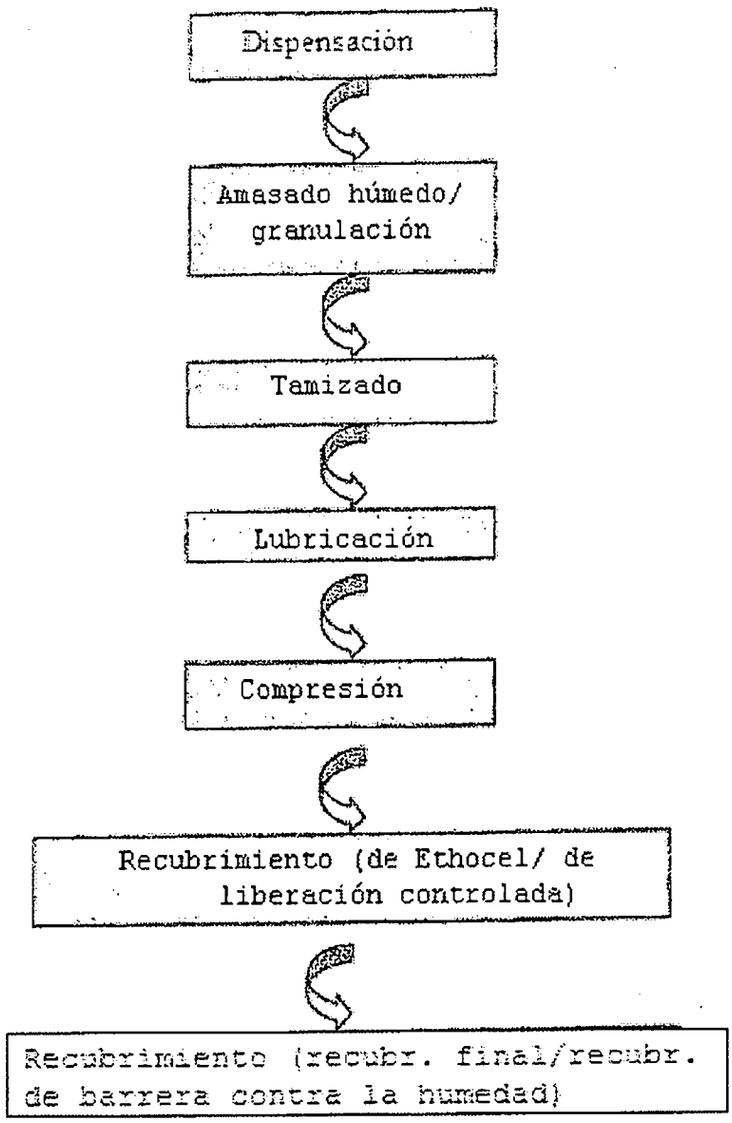
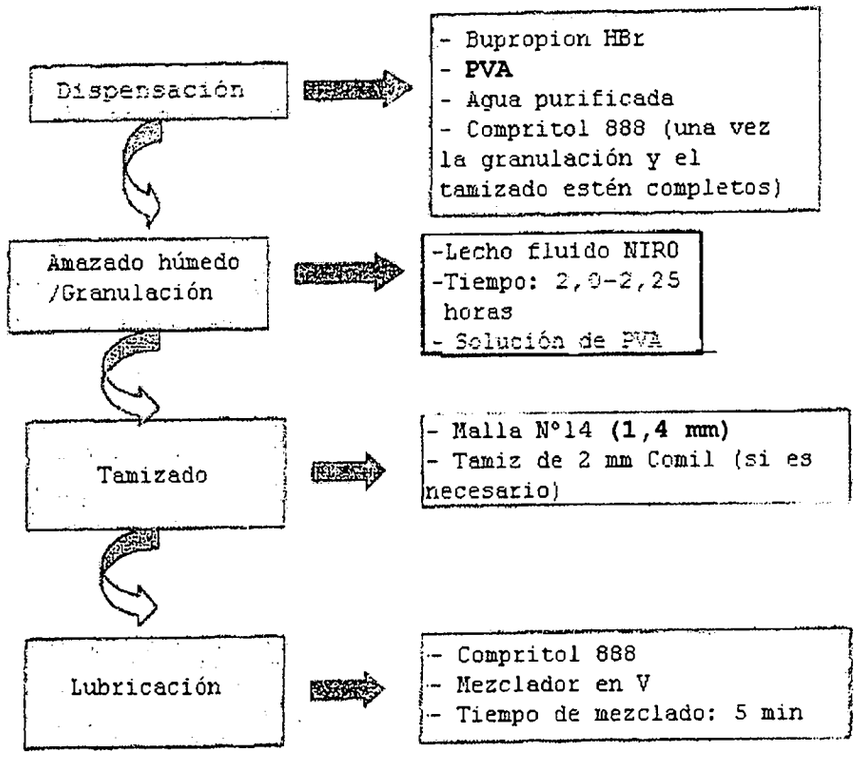

Dispensación
Amasado húmedo/ granulación
Tamizado
Lubricación
Compresión
Recubrimiento (de Ethocel/ de liberación controlada)
Recubrimiento (recubr. final/recubr. de barrera contra la humedad)

FIGURA 12


Dispensación
- Bupropion HBr
- PVA
- Agua purificada
- Compritol 888 (una vez la granulación y el tamizado estén completos)
Amazado húmedo /Granulación
-Lecho fluido NIRO
-Tiempo: 2,0-2,25 horas
- Solución de PVA
Tamizado
- Malla N°14 (1,4 mm)
- Tamiz de 2 mm Comil (si es necesario)
Lubricación
- Compritol 888
- Mezclador en V
- Tiempo de mezclado: 5 min

894

FIGURA 13

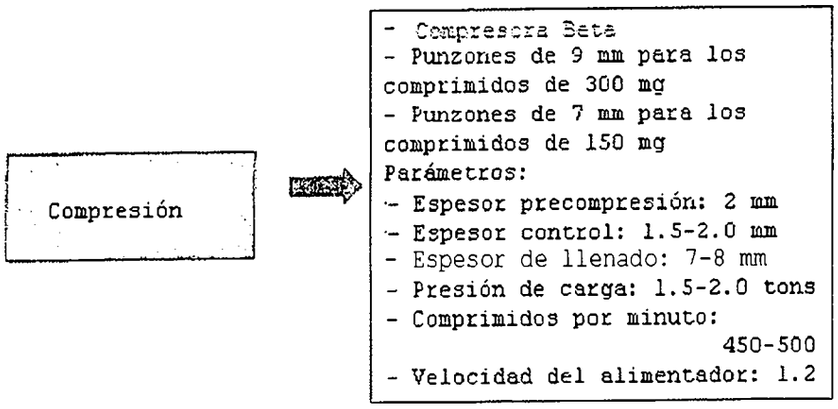


FIGURA 14

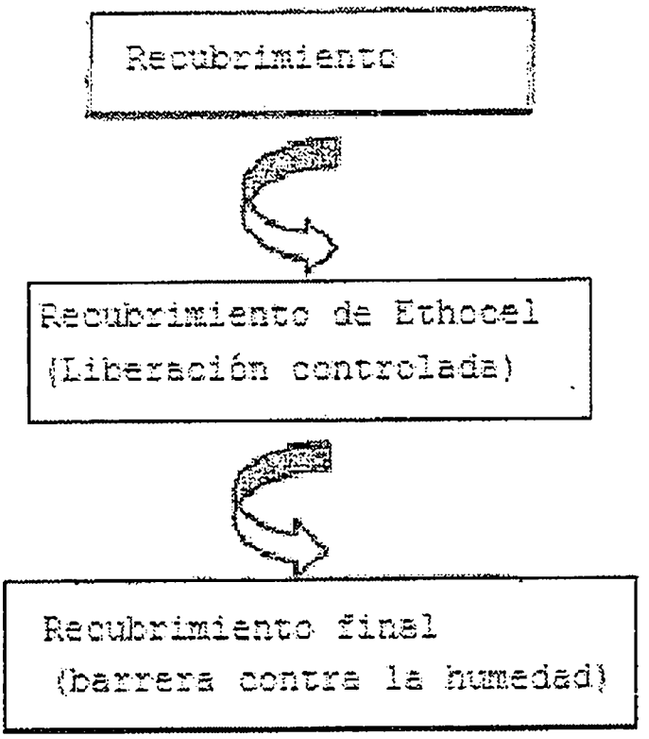

Recubrimiento
Recubrimiento de Ethocel
(Liberación controlada)
Recubrimiento final
(barrera contra la humedad)

FIGURA 15

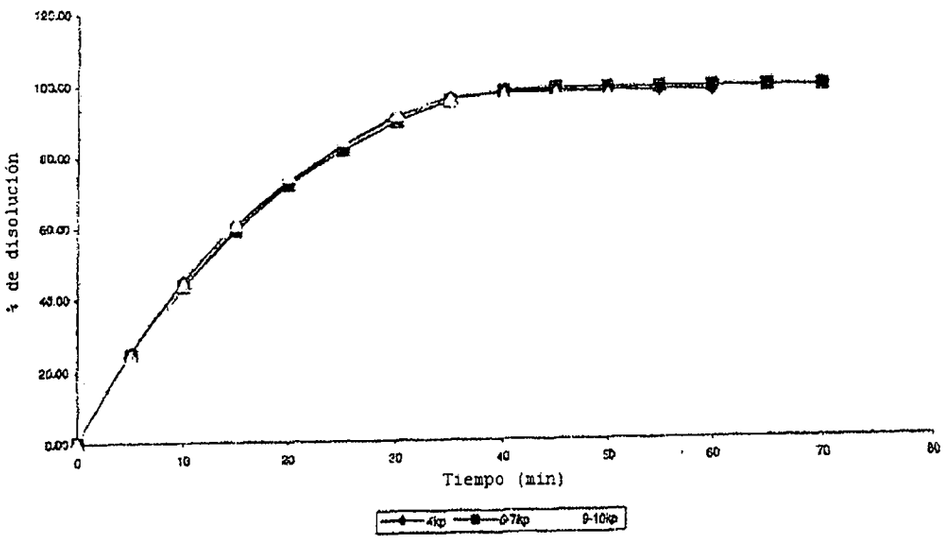

120.00
100.00
80.00
60.00
40.00
20.00
0.00
% de disolución
0
10
20
30
40
50
60
70
80
Tiempo (min)
4kp
6-7kp
8-10kp

FIGURA 16

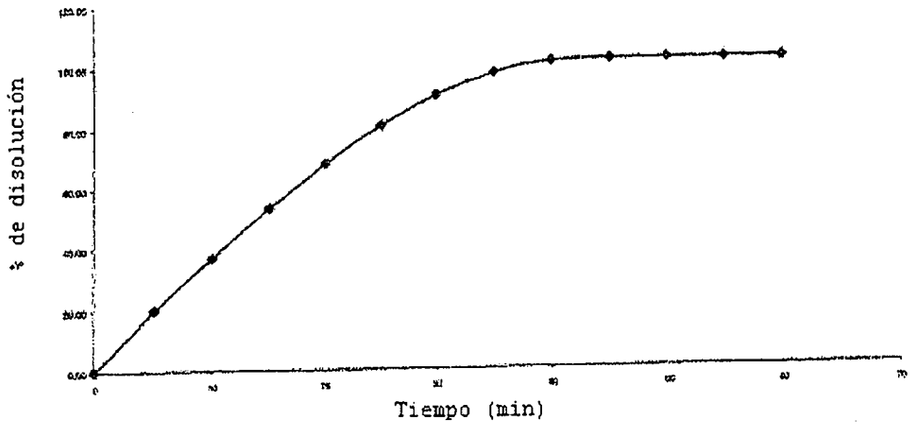


FIGURA 17

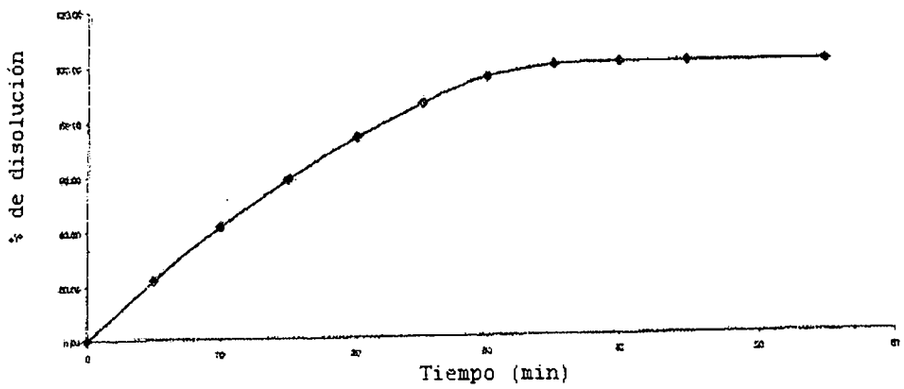


FIGURA 18

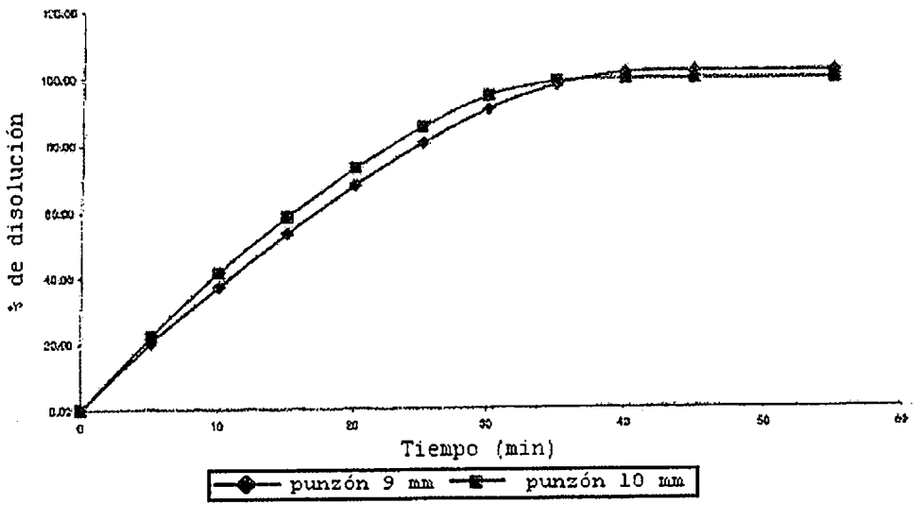


FIGURA 19

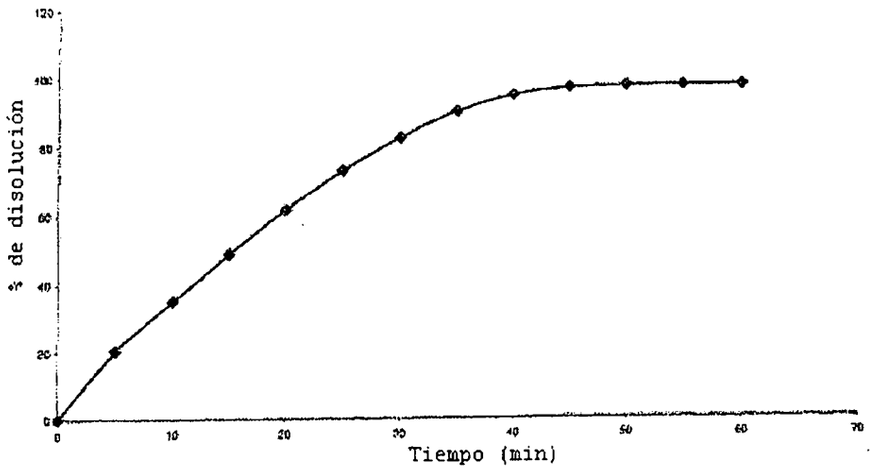


FIGURA 20

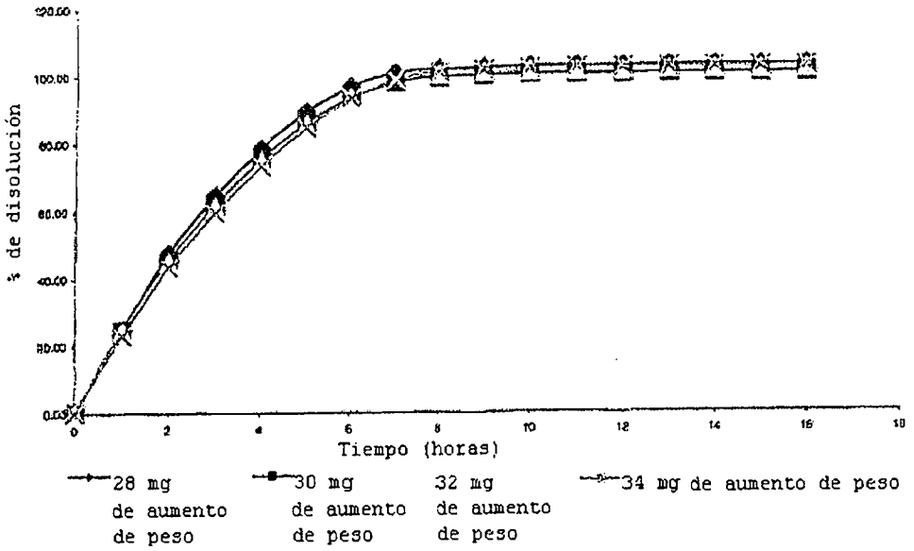

% de disolución
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
2
4
6
8
10
12
14
16
18
Tiempo (horas)
28 mg de aumento de peso
30 mg de aumento de peso
32 mg de aumento de peso
34 mg de aumento de peso

FIGURA 21

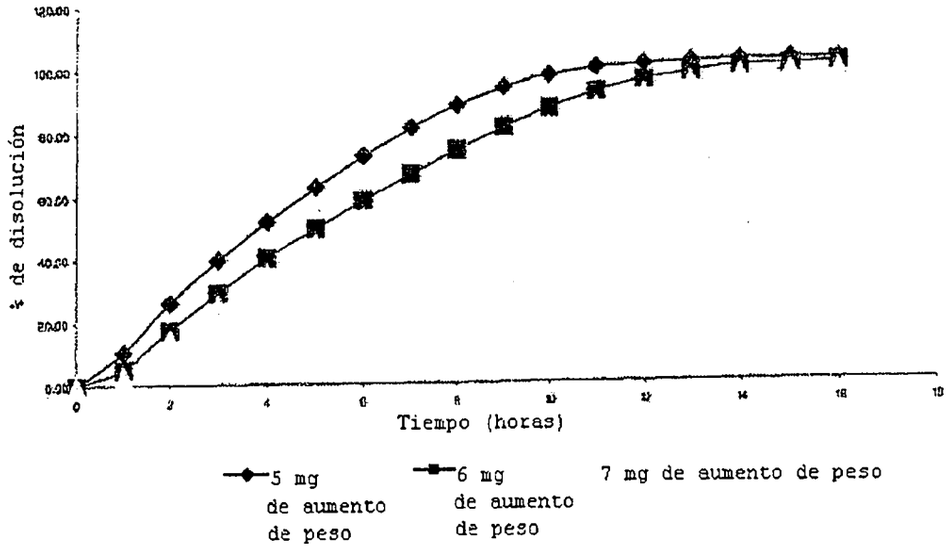

% de disolución
Tiempo (horas)
5 mg de aumento de peso
6 mg de aumento de peso
7 mg de aumento de peso

FIGURA 22

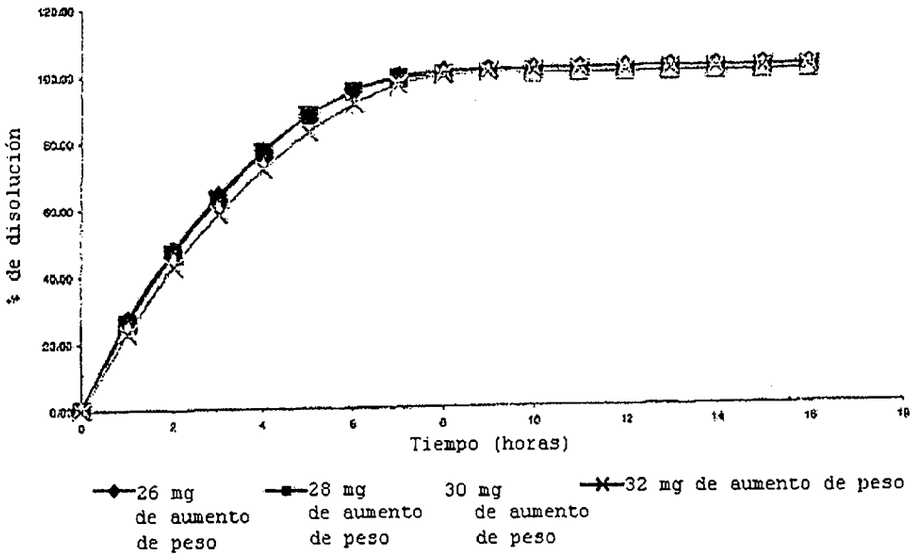

% de disolución
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
2
4
6
8
10
12
14
16
18
Tiempo (horas)
26 mg de aumento de peso
28 mg de aumento de peso
30 mg de aumento de peso
32 mg de aumento de peso

FIGURA 23

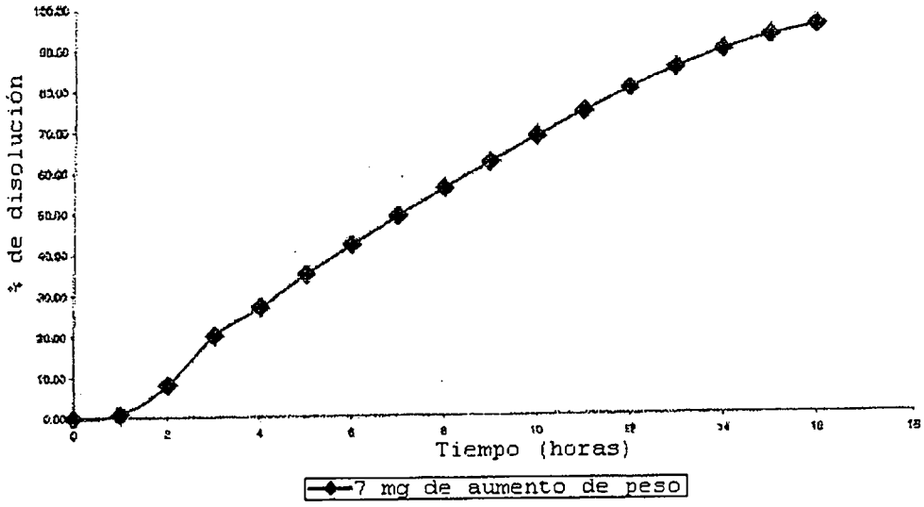


FIGURA 24

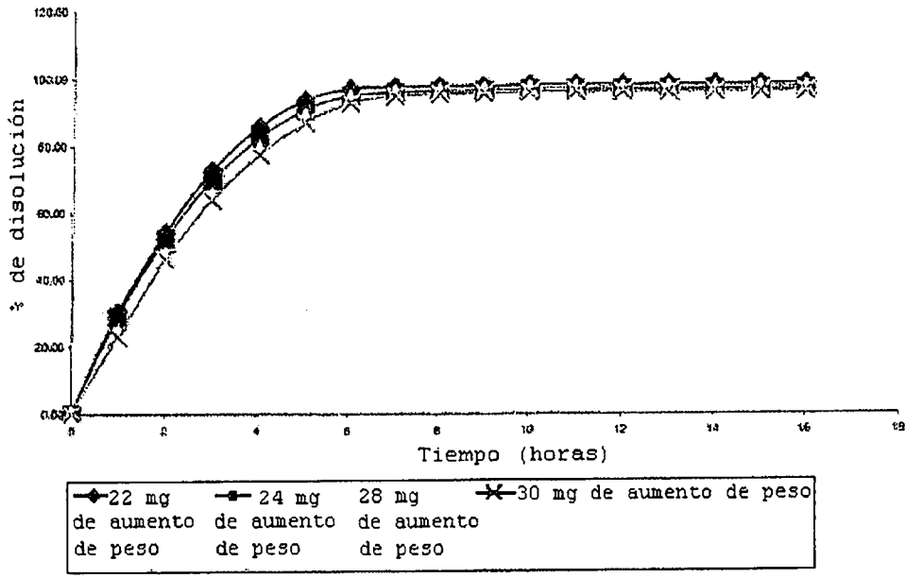

% de disolución
Tiempo (horas)
22 mg de aumento de peso
24 mg de aumento de peso
28 mg de aumento de peso
30 mg de aumento de peso

FIGURA 25

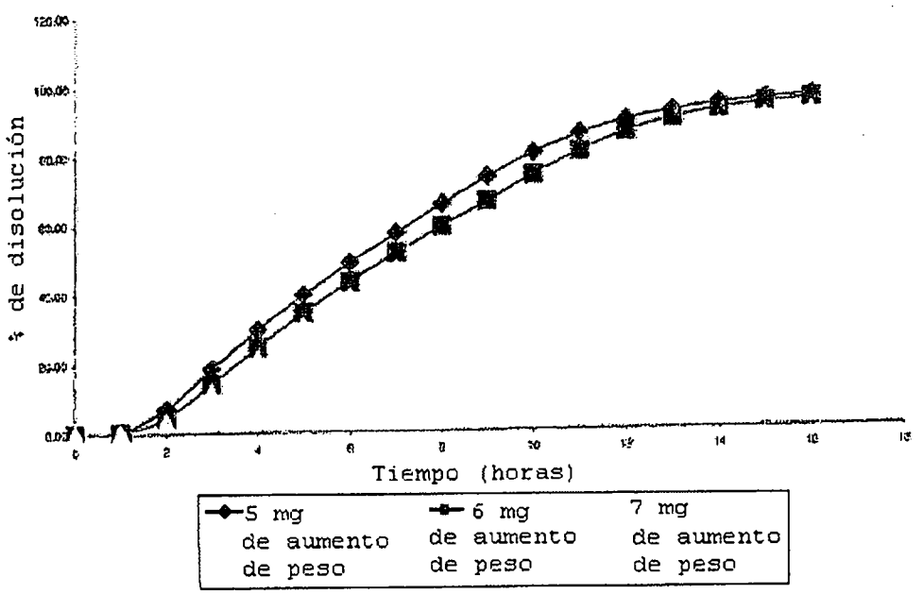

% de disolución
Tiempo (horas)
5 mg de aumento de peso
6 mg de aumento de peso
7 mg de aumento de peso

FIGURA 26

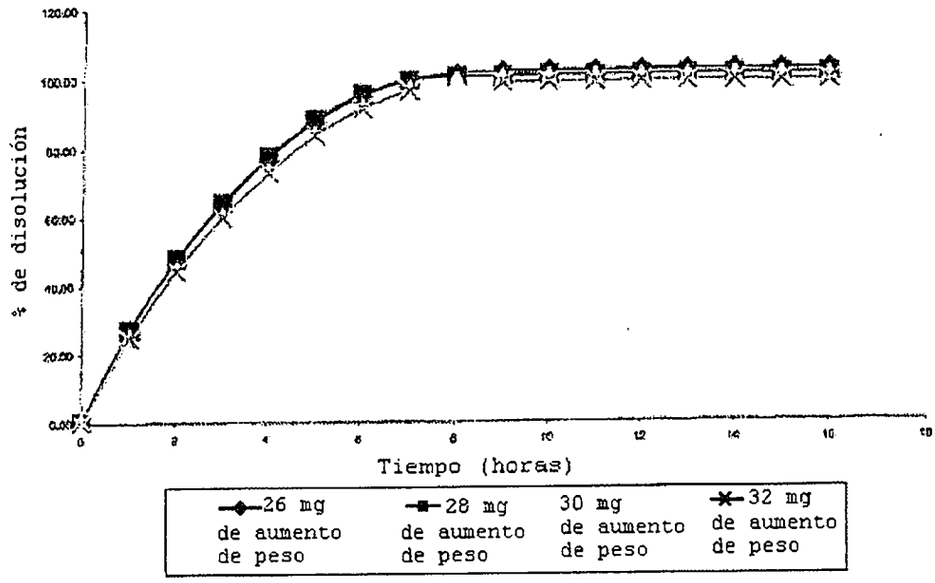

% de disolución
Tiempo (horas)
26 mg de aumento de peso
28 mg de aumento de peso
30 mg de aumento de peso
32 mg de aumento de peso

FIGURA 27

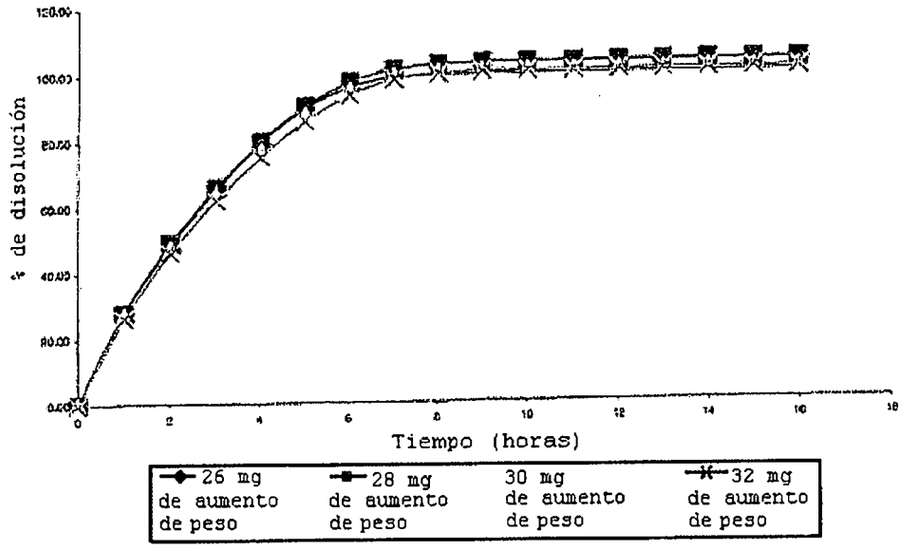

% de disolución
Tiempo (horas)
26 mg de aumento de peso
28 mg de aumento de peso
30 mg de aumento de peso
32 mg de aumento de peso

FIGURA 28

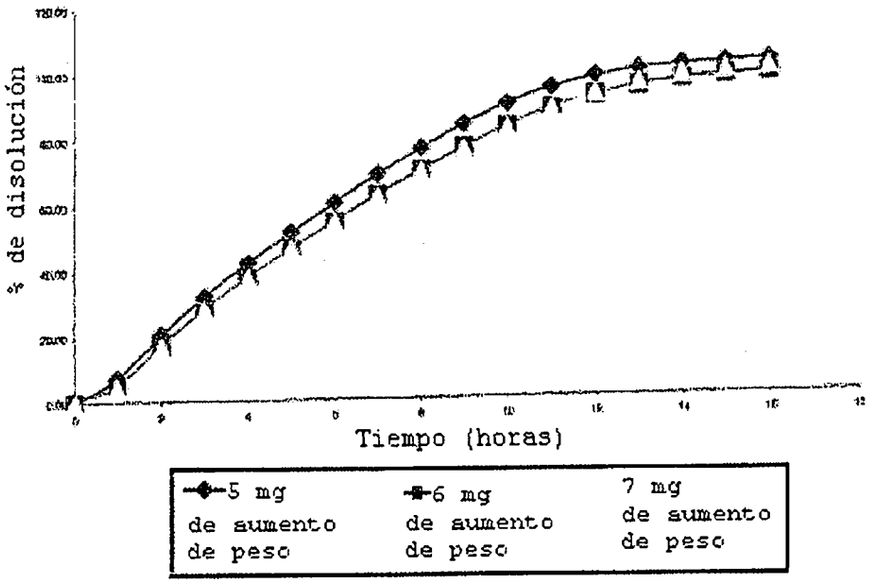

% de disolución
Tiempo (horas)
5 mg de aumento de peso
6 mg de aumento de peso
7 mg de aumento de peso

FIGURA 29

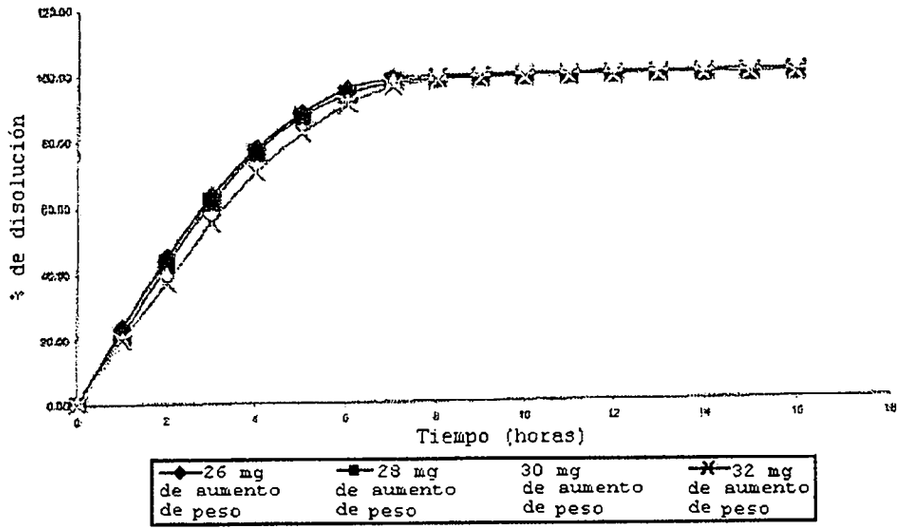

% de disolución
Tiempo (horas)
26 mg de aumento de peso
28 mg de aumento de peso
30 mg de aumento de peso
32 mg de aumento de peso

FIGURA 30

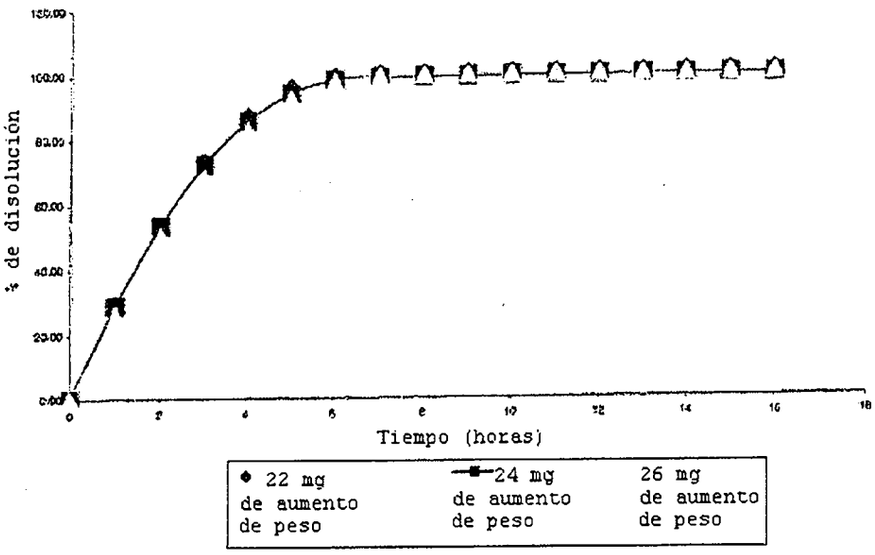

% de disolución
Tiempo (horas)
22 mg de aumento de peso
24 mg de aumento de peso
26 mg de aumento de peso

FIGURA 31

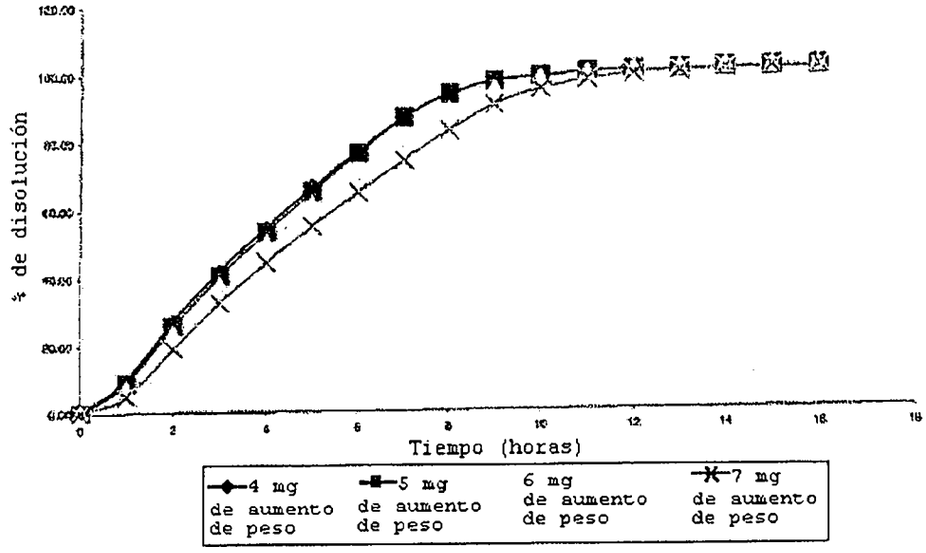

% de disolución
Tiempo (horas)
4 mg de aumento de peso
5 mg de aumento de peso
6 mg de aumento de peso
7 mg de aumento de peso

FIGURA 32

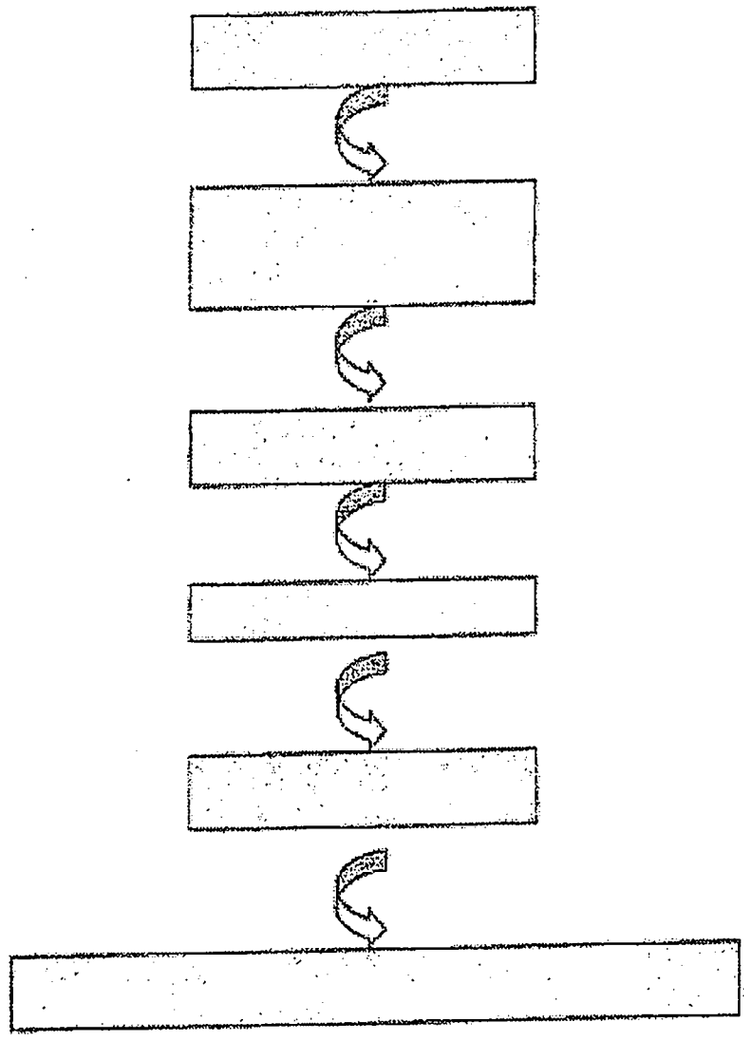


FIGURA 33

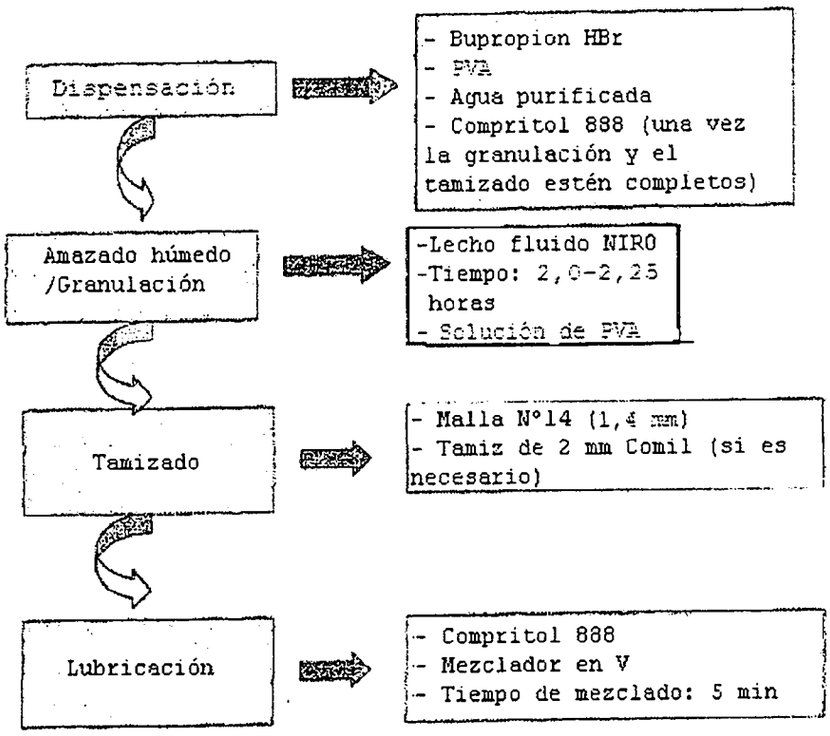

Dispensación
- Bupropion HBr
- PVA
- Agua purificada
- Compritol 888 (una vez la granulación y el tamizado estén completos)
Amazado húmedo /Granulación
-Lecho fluido NIRO
-Tiempo: 2,0-2,25 horas
- Solución de PVA
Tamizado
- Malla N°14 (1,4 mm)
- Tamiz de 2 mm Comil (si es necesario)
Lubricación
- Compritol 888
- Mezclador en V
- Tiempo de mezclado: 5 min

FIGURA 34

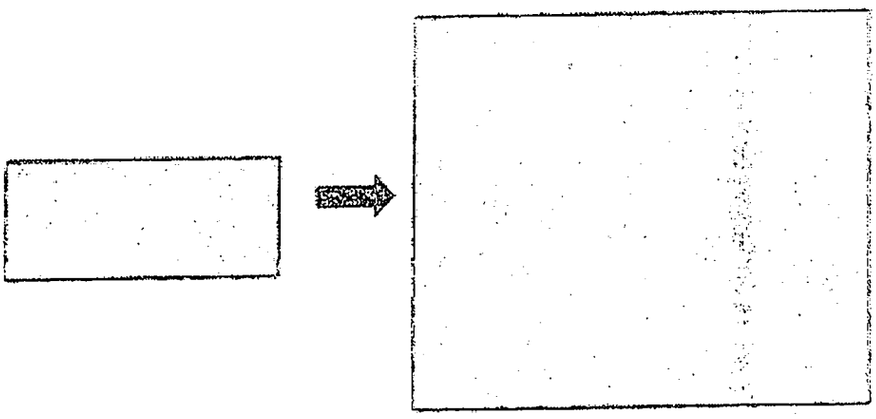


FIGURA 35

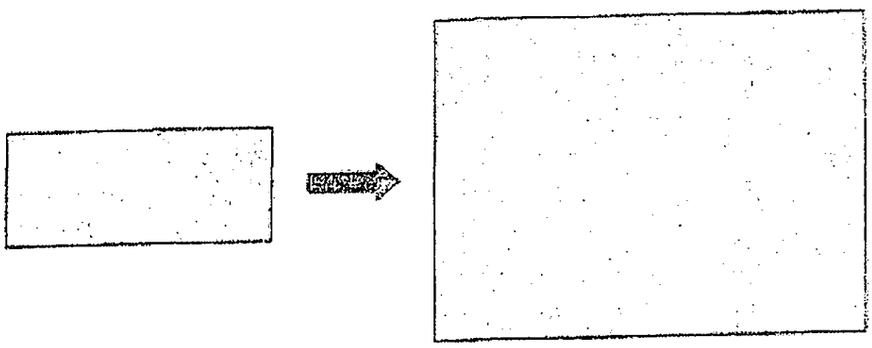


FIGURA 36

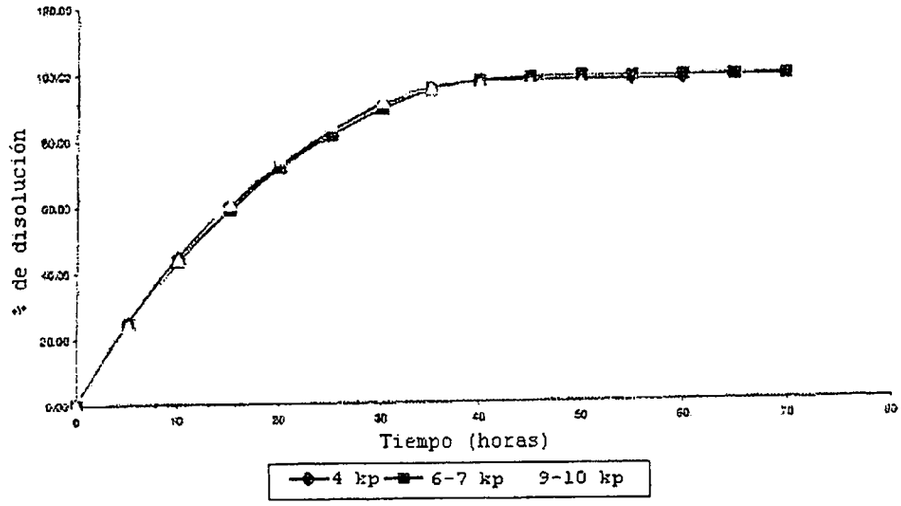


FIGURA 37

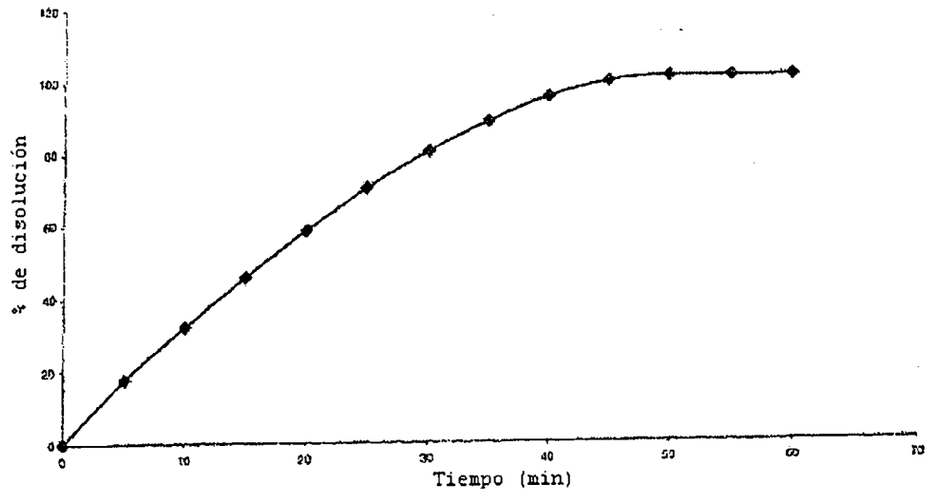


FIGURA 38

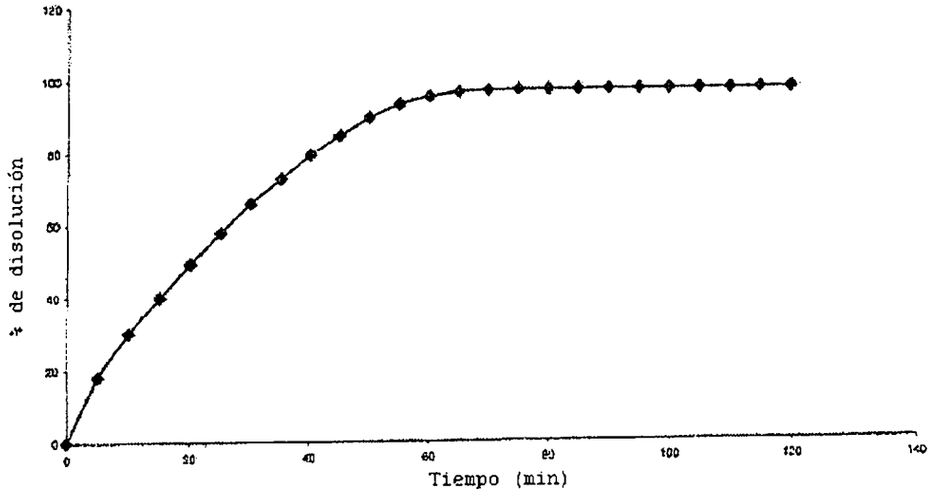


FIGURA 39

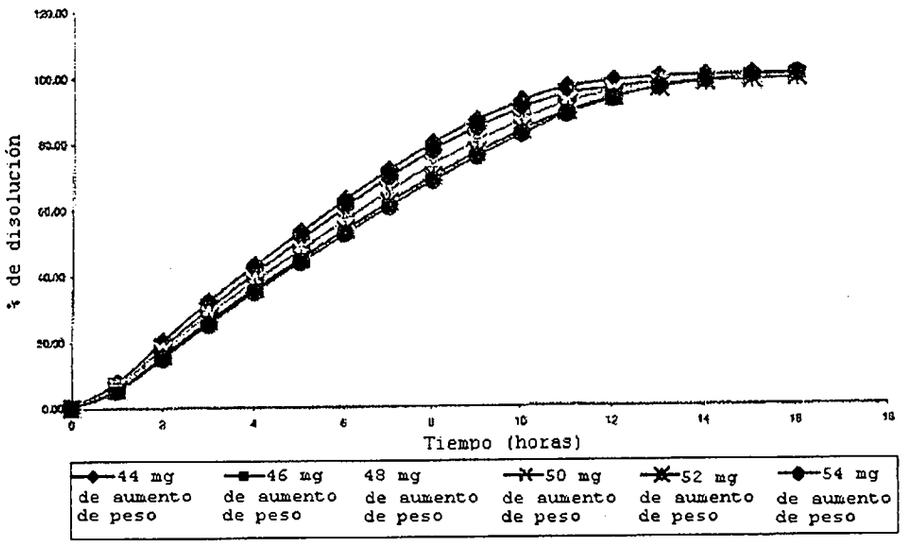

% de disolución
120.00
100.00
80.00
60.00
40.00
20.00
0.00
0
2
4
6
8
10
12
14
16
18
Tiempo (horas)
44 mg de aumento de peso
46 mg de aumento de peso
48 mg de aumento de peso
50 mg de aumento de peso
52 mg de aumento de peso
54 mg de aumento de peso

FIGURA 40

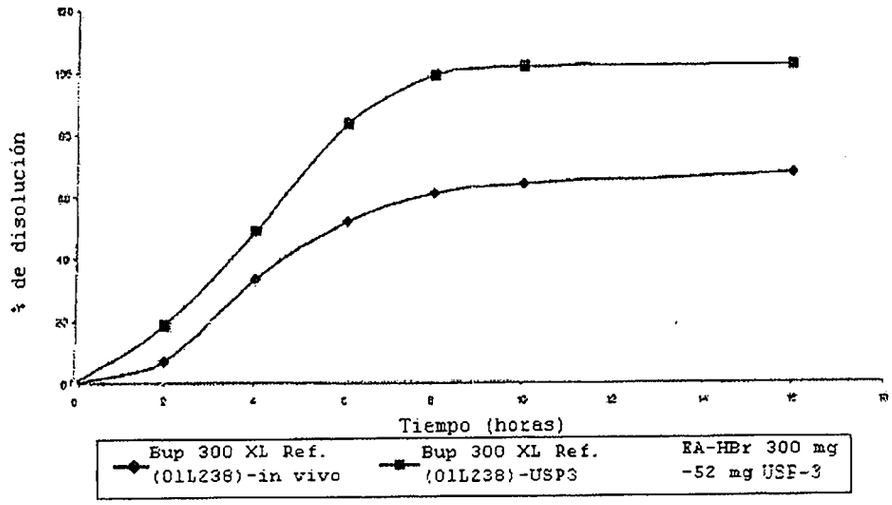

% de disolución
Tiempo (horas)
Bup 300 XL Ref. (01L238)-in vivo
Bup 300 XL Ref. (01L238)-USP3
EA-HBr 300 mg -52 mg USP-3

FIGURA 41

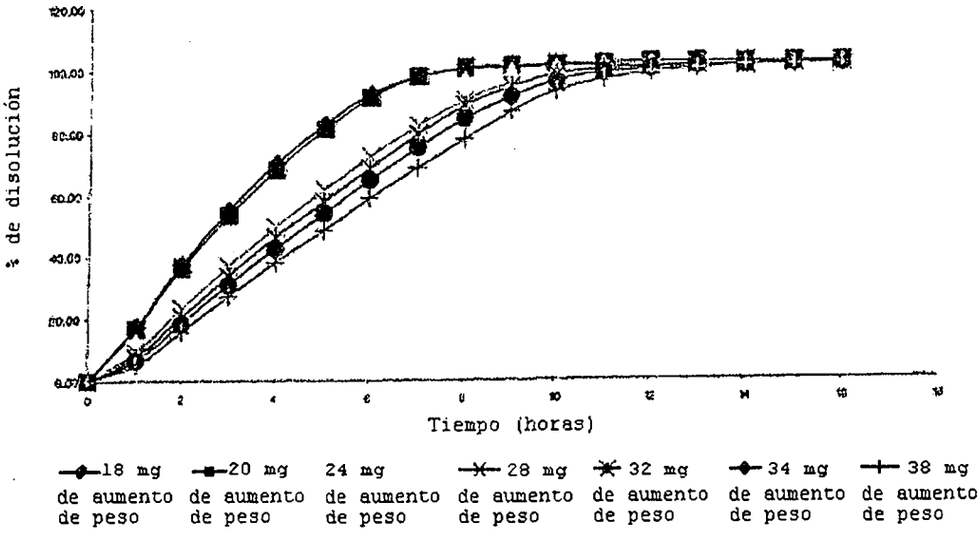

% de disolución
Tiempo (horas)
18 mg de aumento de peso
20 mg de aumento de peso
24 mg de aumento de peso
28 mg de aumento de peso
32 mg de aumento de peso
34 mg de aumento de peso
38 mg de aumento de peso

FIGURA 42

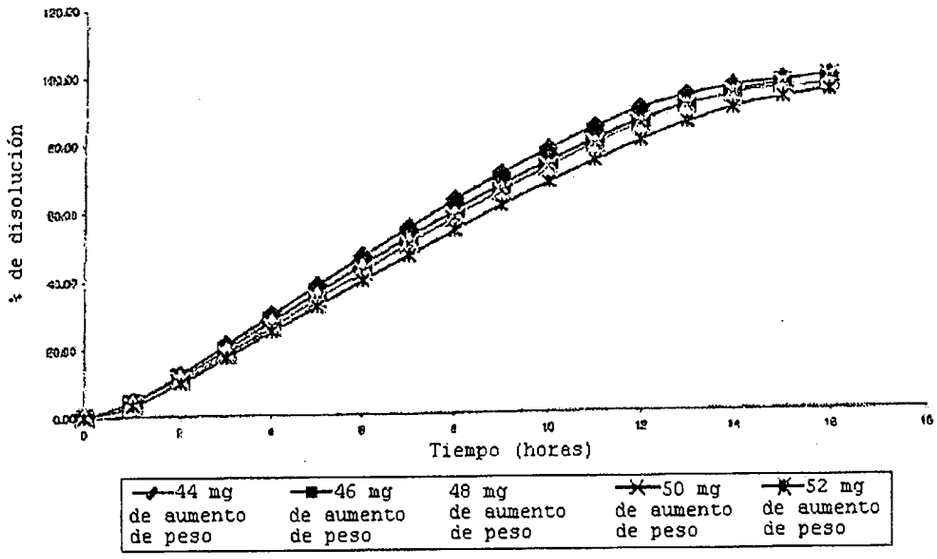

% de disolución
Tiempo (horas)
44 mg de aumento de peso
46 mg de aumento de peso
48 mg de aumento de peso
50 mg de aumento de peso
52 mg de aumento de peso

FIGURA 43

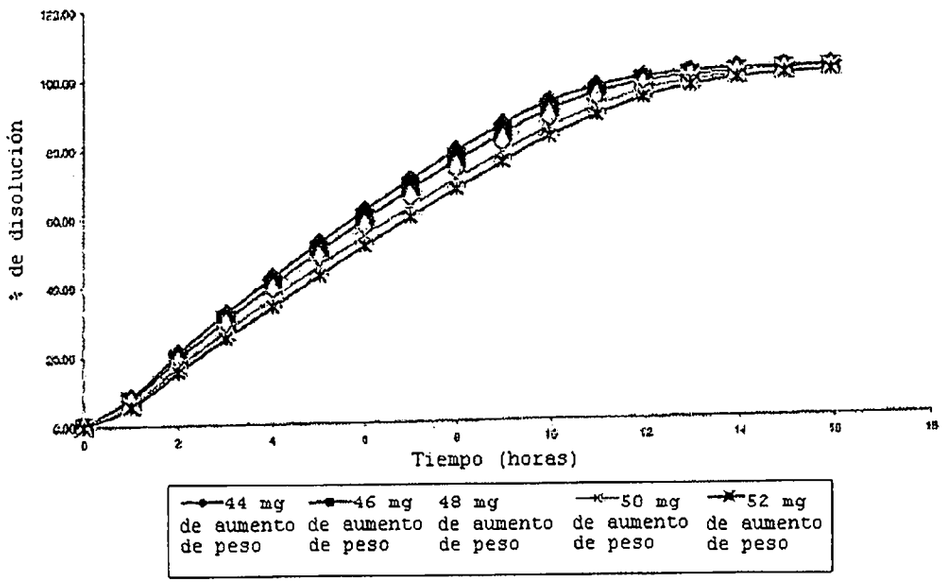

% de disolución
Tiempo (horas)
44 mg de aumento de peso
46 mg de aumento de peso
48 mg de aumento de peso
50 mg de aumento de peso
52 mg de aumento de peso

FIGURA 44

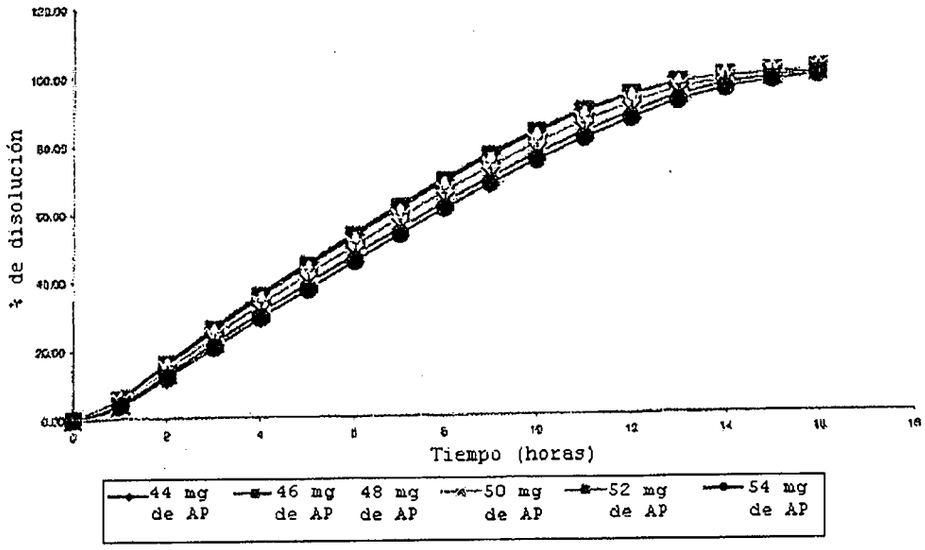

% de disolución
Tiempo (horas)
44 mg de AP
46 mg de AP
48 mg de AP
50 mg de AP
52 mg de AP
54 mg de AP

FIGURA 45

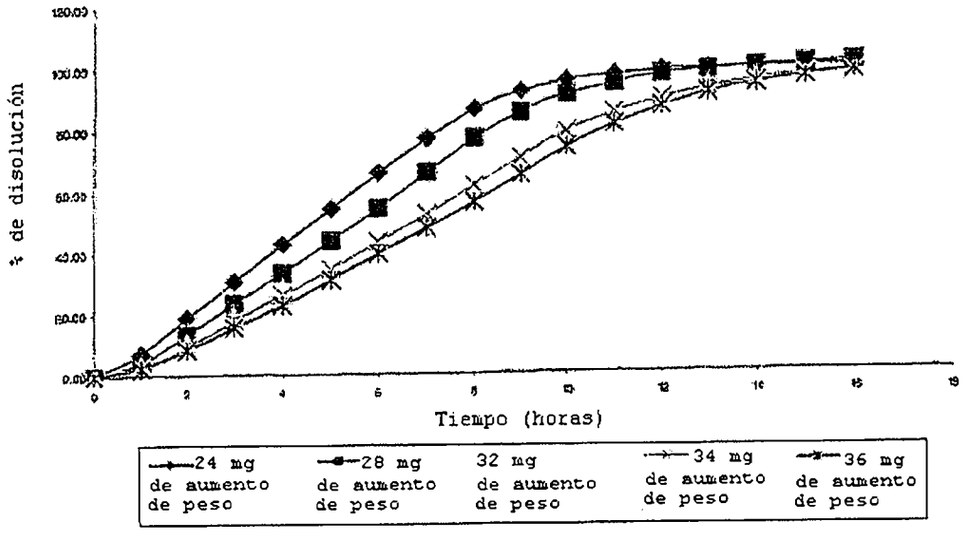

% de disolución
Tiempo (horas)
24 mg de aumento de peso
28 mg de aumento de peso
32 mg de aumento de peso
34 mg de aumento de peso
36 mg de aumento de peso

FIGURA 46

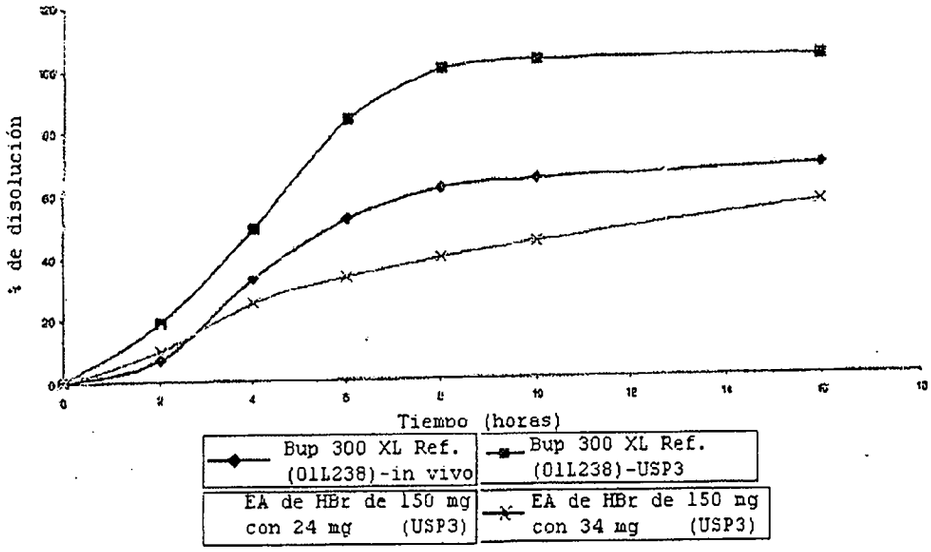

% de disolución
Tiempo (horas)
Bup 300 XL Ref. (01L238)-in vivo
Bup 300 XL Ref. (01L238)-USP3
EA de HBr de 150 mg con 24 mg (USP3)
EA de HBr de 150 mg con 34 mg (USP3)

FIGURA 47

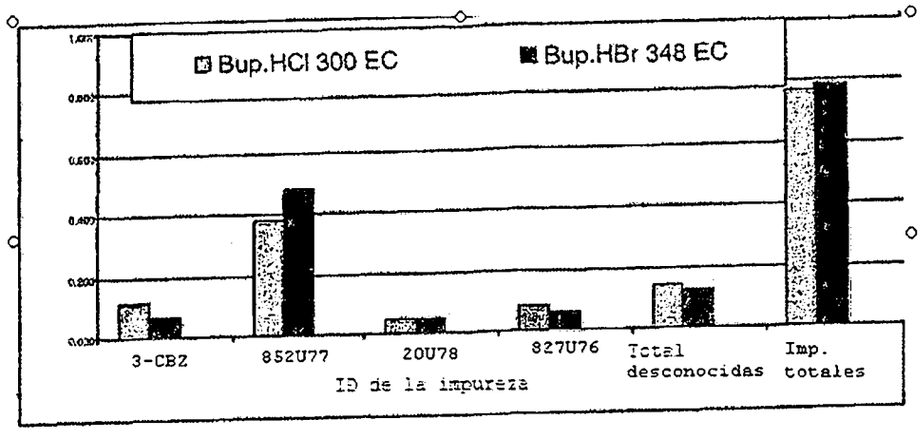

Bup.HCl 300 EC
Bup.HBr 348 EC
3-CBZ
852U77
20U78
827U76
Total desconocidas
Imp. totales
ID de la impureza

FIGURA 48

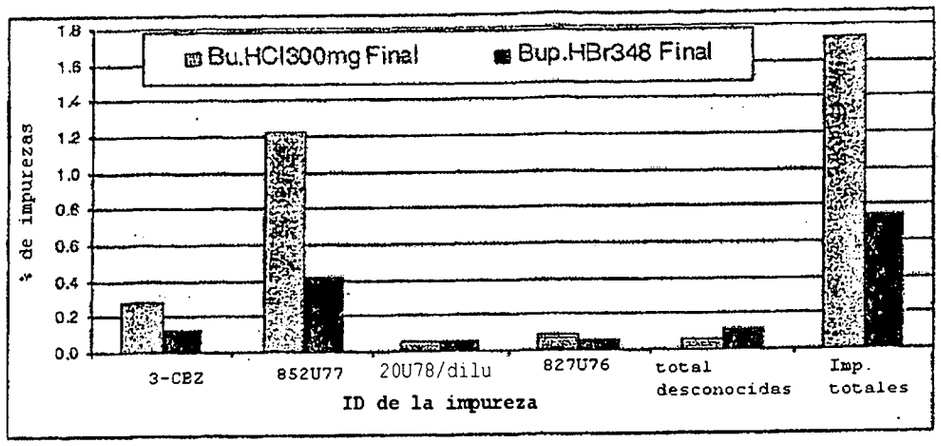

Bu.HCl300mg Final
Bup.HBr348 Final
% de impurezas
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
3-CBZ
852U77
20U78/dilu
827U76
total desconocidas
Imp. totales
ID de la impureza

FIGURA 49

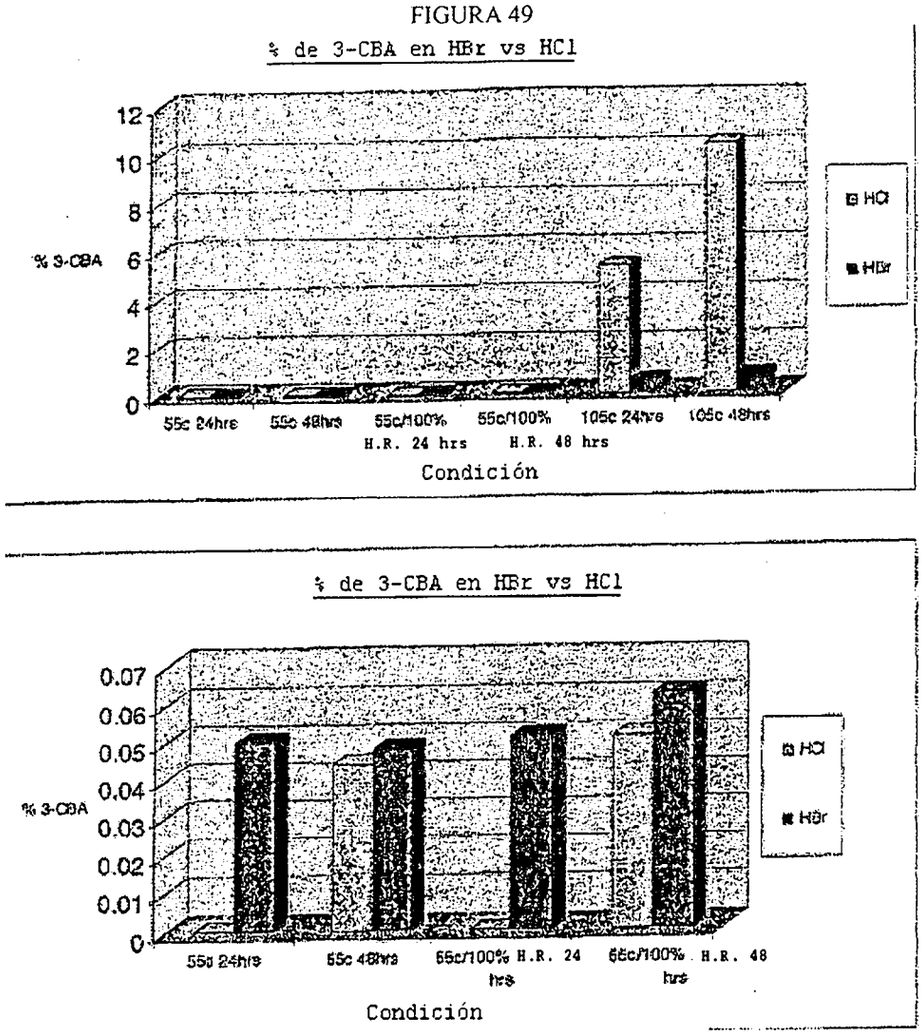
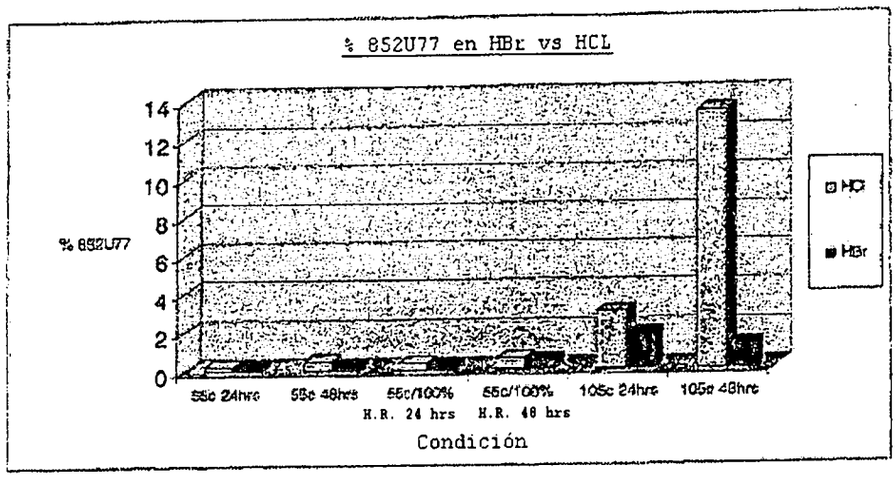

% de 3-CBA en HBr vs HCl
% 3-CBA
12
10
8
6
4
2
0
55c 24hrs
55c 48hrs
55c/100% H.R. 24 hrs
55c/100% H.R. 48 hrs
105c 24hrs
105c 48hrs
Condición
HCl
HBr
% de 3-CBA en HBr vs HCl
% 3-CBA
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
55c 24hrs
55c 48hrs
65c/100% H.R. 24 hrs
65c/100% H.R. 48 hrs
Condición
HCl
HBr

FIGURA 50


% 852U77 en HBr vs HCL
14
12
10
8
6
4
2
0
% 852U77
55c 24hrs
55c 48hrs
55c/100% H.R. 24 hrs
55c/100% H.R. 48 hrs
105c 24hrs
105c 48hrs
HCl
HBr
Condición

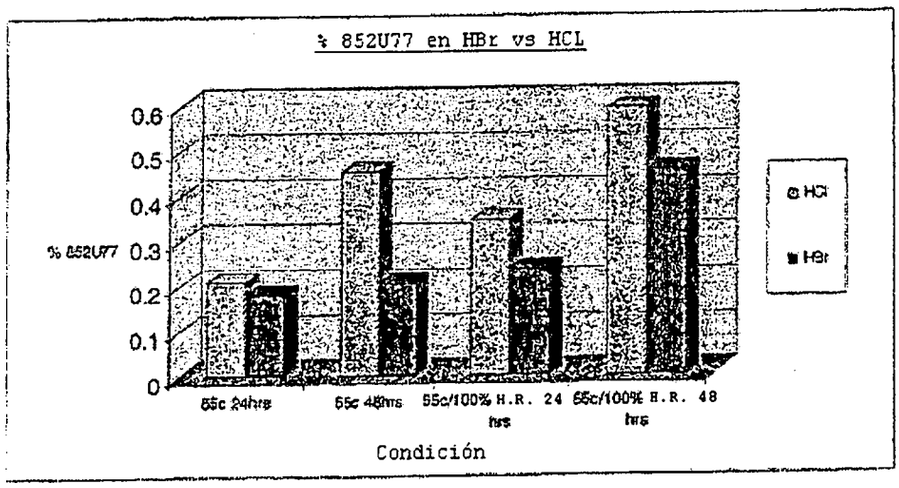
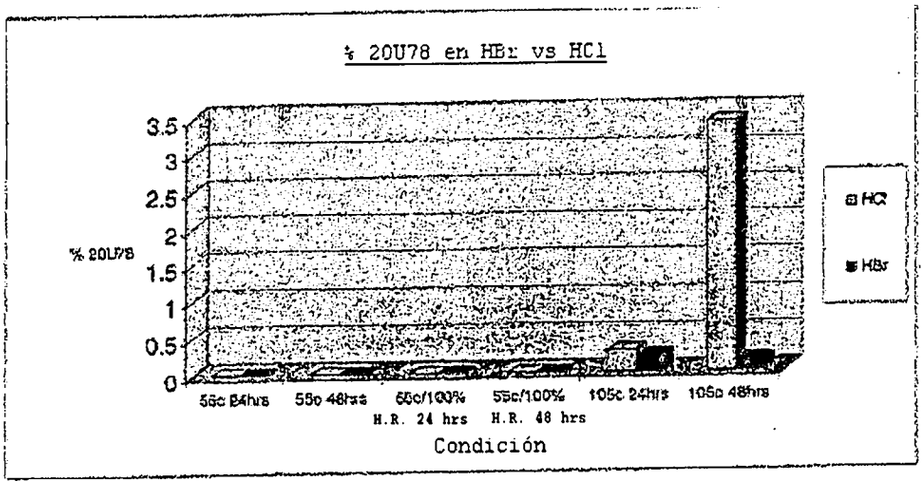

% 852U77 en HBr vs HCL
0.6
0.5
0.4
0.3
0.2
0.1
0
% 852U77
55c 24hrs
55c 48hrs
55c/100% H.R. 24 hrs
55c/100% H.R. 48 hrs
HCl
HBr
Condición

FIGURA 51


% 20U78 en HBr vs HCl
3.5
3
2.5
2
1.5
1
0.5
0
% 20U78
HCl
HBr
55c 24hrs
55c 48hrs
60c/100% H.R. 24 hrs
55c/100% H.R. 48 hrs
105c 24hrs
105c 48hrs
Condición

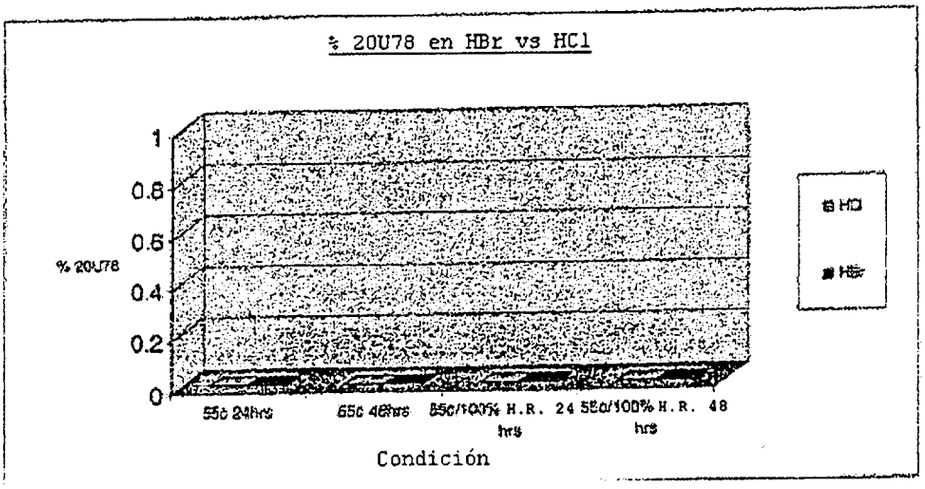
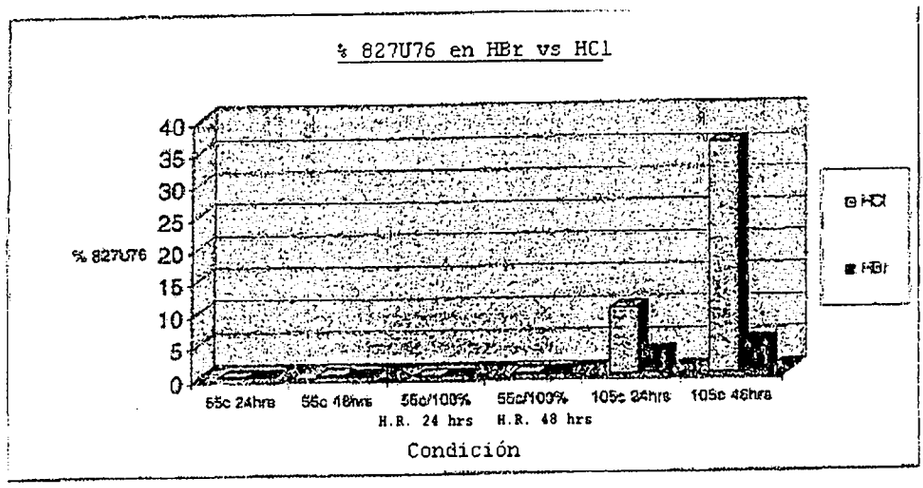

% 20U78 en HBr vs HCl
1
0.8
0.6
0.4
0.2
0
% 20U78
HCl
HBr
55c 24hrs
65c 48hrs
85c/100% H.R. 24 hrs
85c/100% H.R. 48 hrs
Condición

FIGURA 52


% 827U76 en HBr vs HCl
40
35
30
25
% 827U76 20
15
10
5
0
55c 24hrs
55c 48hrs
55c/100% H.R. 24 hrs
55c/100% H.R. 48 hrs
105c 24hrs
105c 48hrs
Condición
HCl
HBr

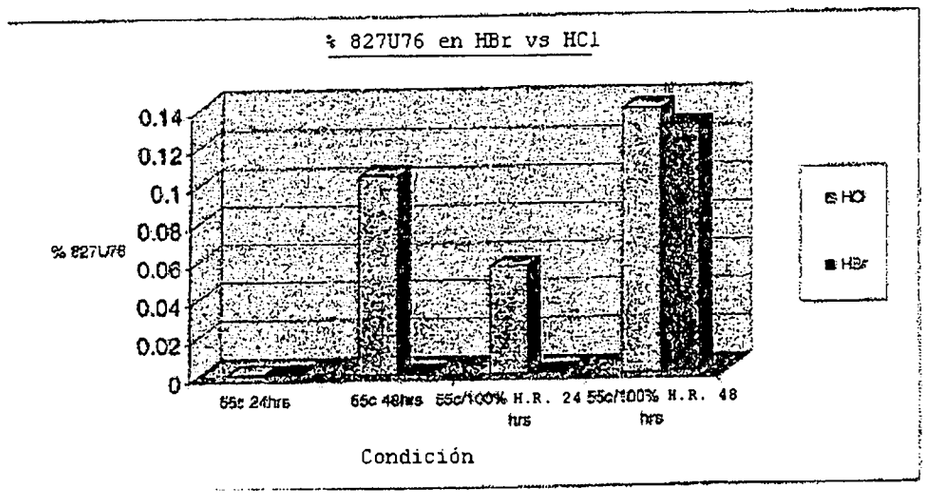

% 827U76 en HBr vs HCl
0.14
0.12
0.1
0.08
% 827U76 0.06
0.04
0.02
0
55c 24hrs
65c 48hrs
55c/100% H.R. 24 hrs
55c/100% H.R. 48 hrs
Condición
HCl
HBr

FIGURA 53

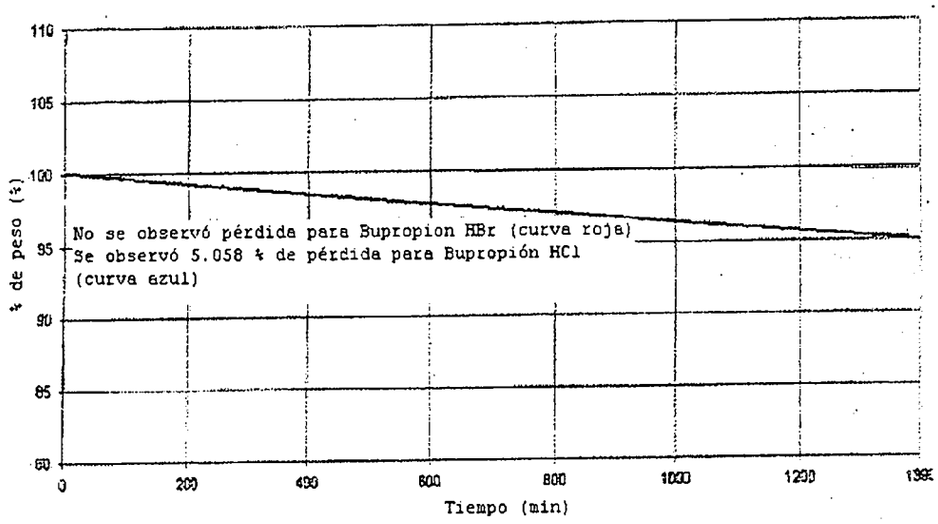
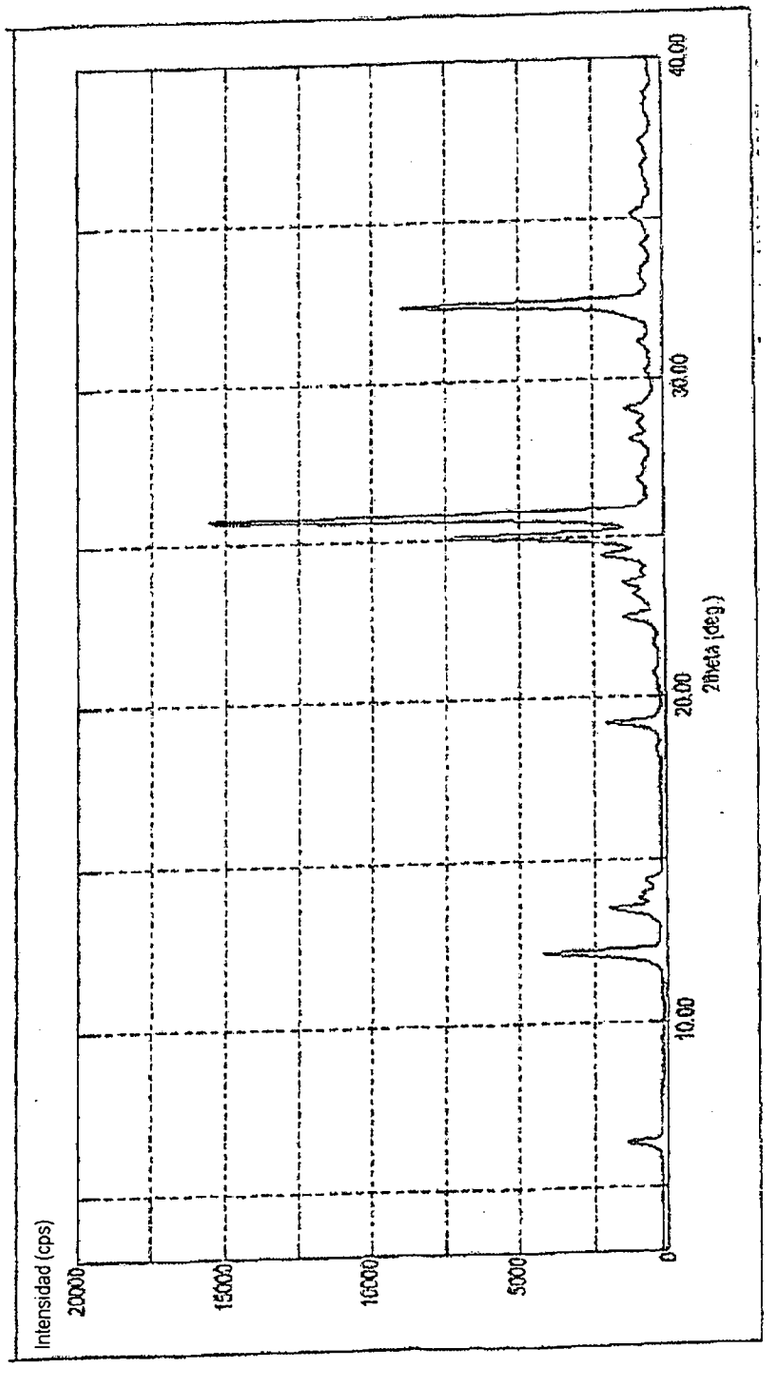

110
105
100
95
90
85
80
% de peso (%)
No se observó pérdida para Bupropion HBr (curva roja)
Se observó 5.058 % de pérdida para Bupropión HCl
(curva azul)
0
200
400
600
800
1000
1200
Tiempo (min)

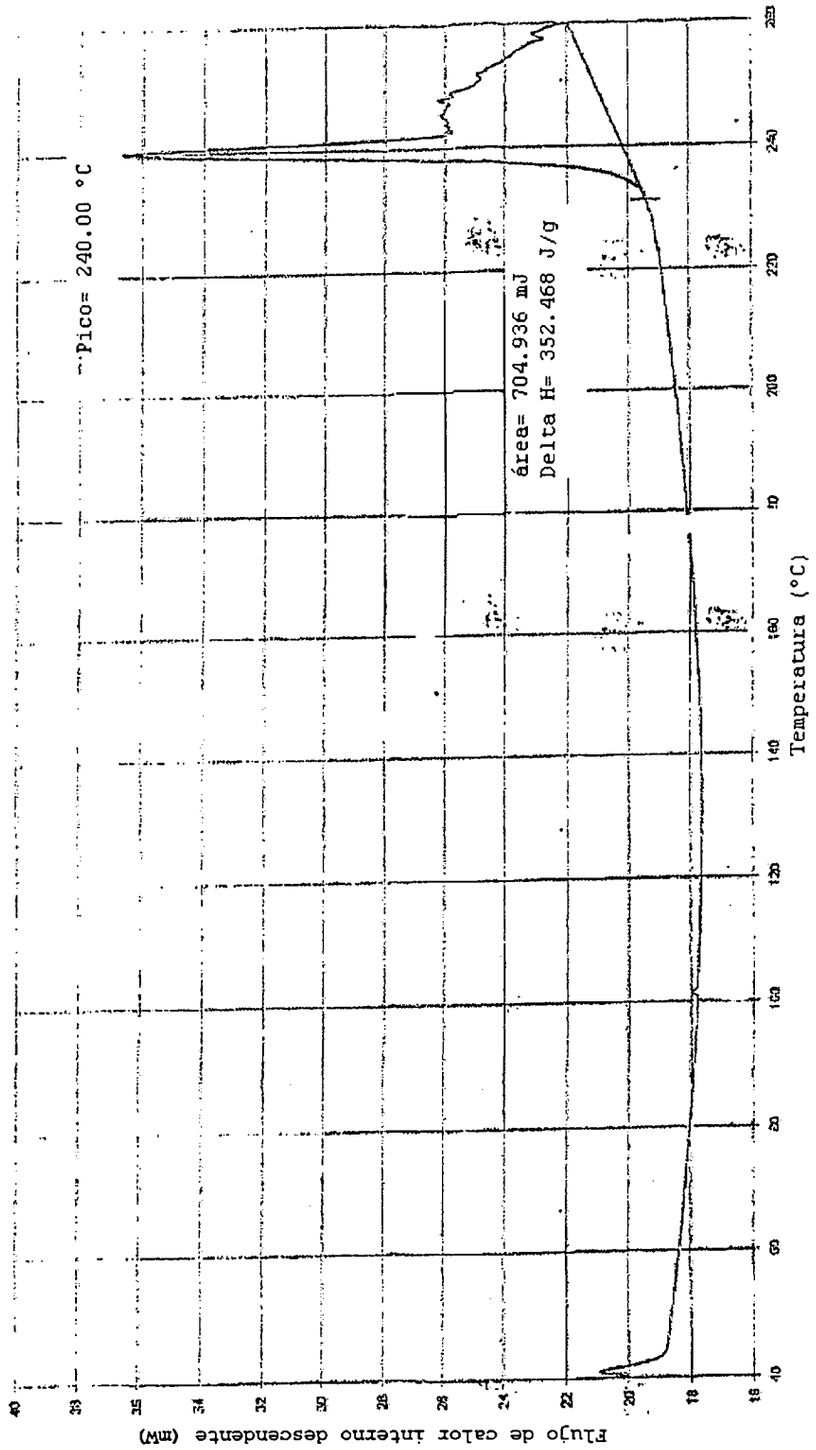
FIGURA 54



PXRD de la forma polimórfica I de Bromhidrato de bupropion

INFORMACIÓN CONFIDENCIAL

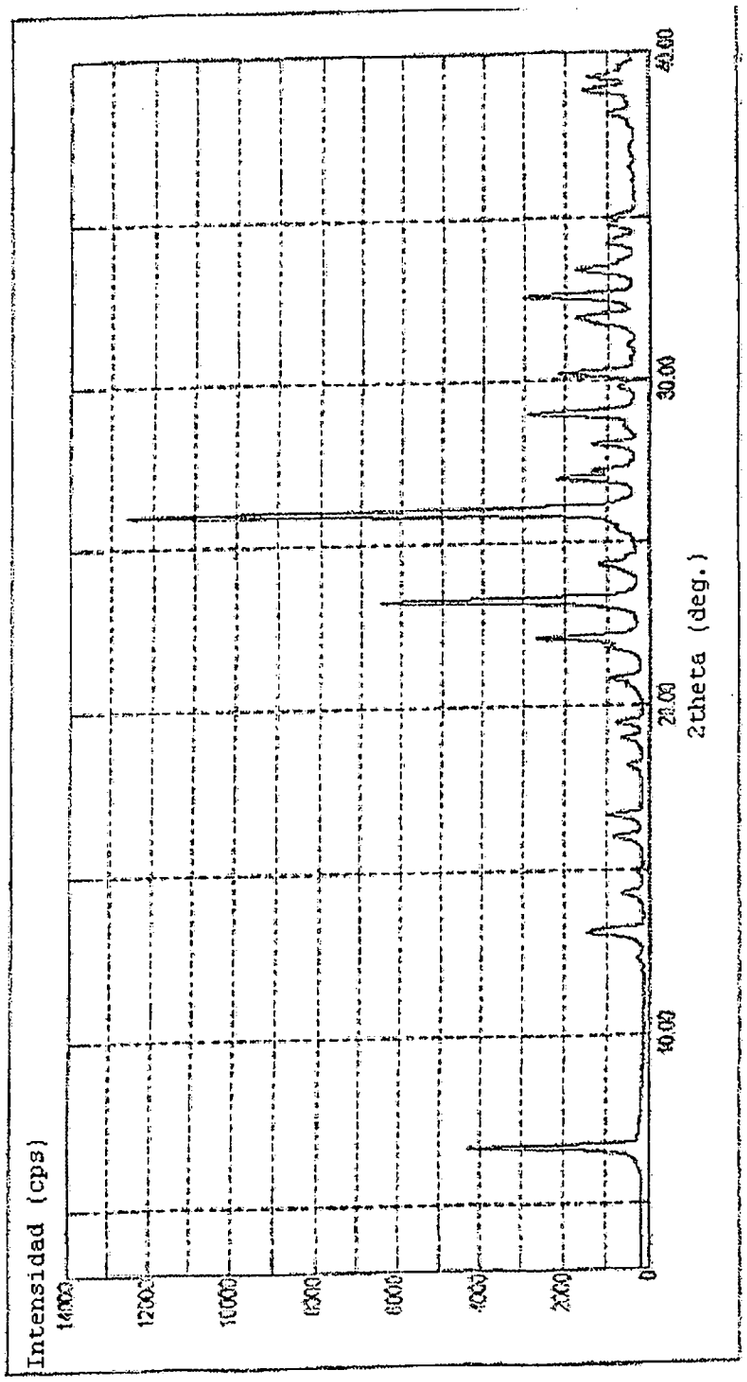
FIGURA 55



DSC de la forma polimórfica I de bromhidrato de Bupropion

INFORMACIÓN CONFIDENCIAL

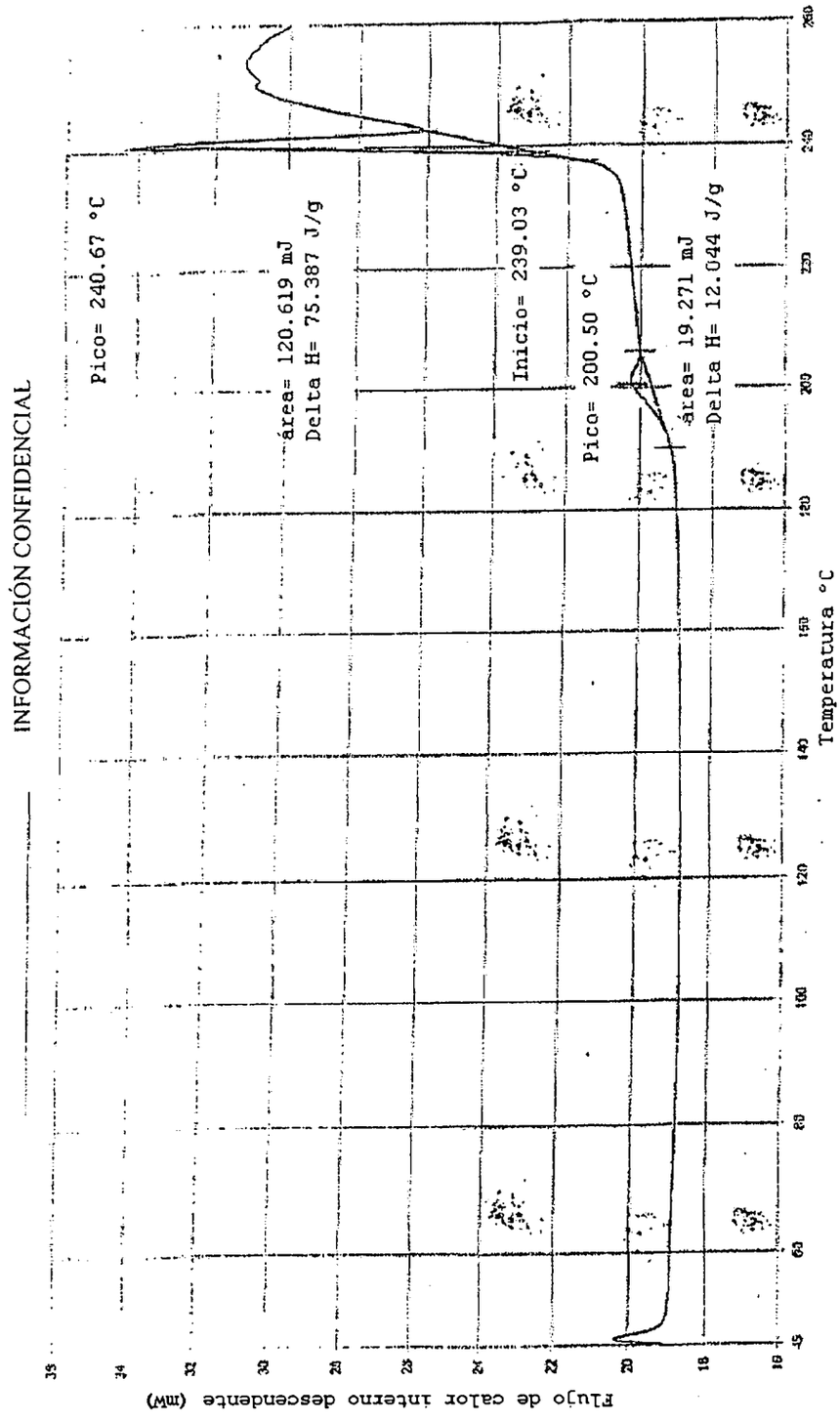
FIGURA 56



PXRD de la forma polimórfica II de bromhidrato de bupropion

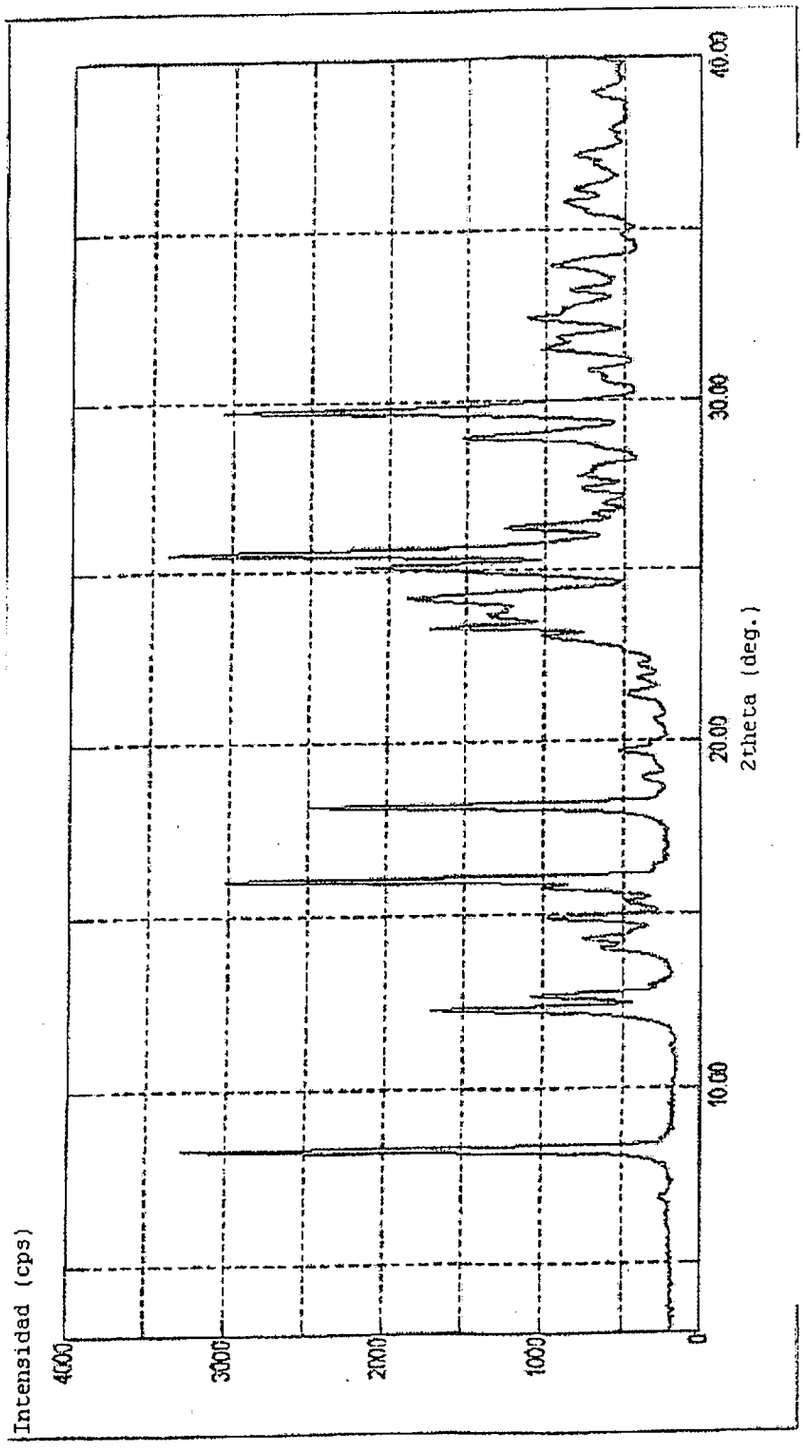
INFORMACIÓN CONFIDENCIAL

FIGURA 57



DSC de la forma polimórfica II de Bromhidrato de bupropion

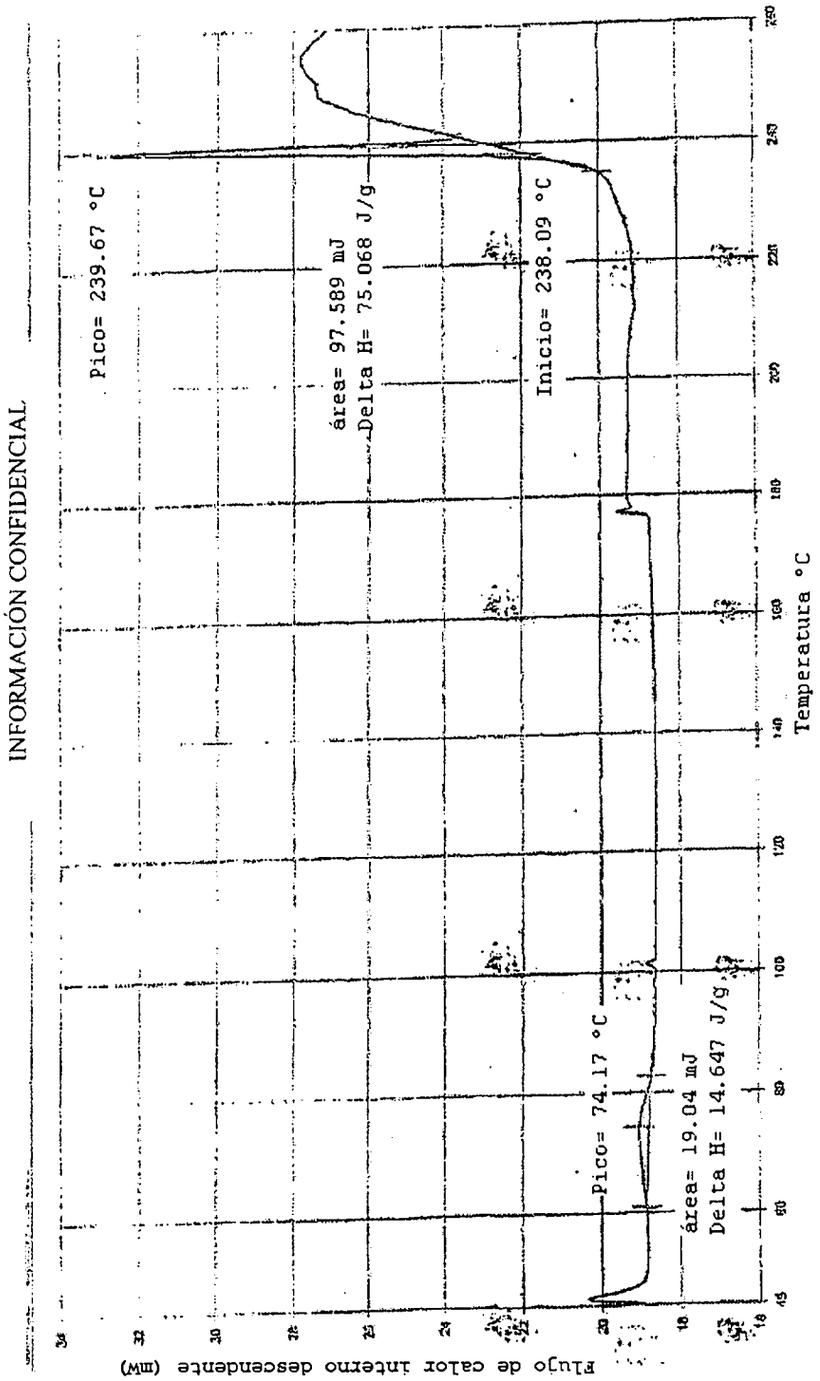
FIGURA 58



PXRD de la forma polimórfica III de bromhidrato de bupropion

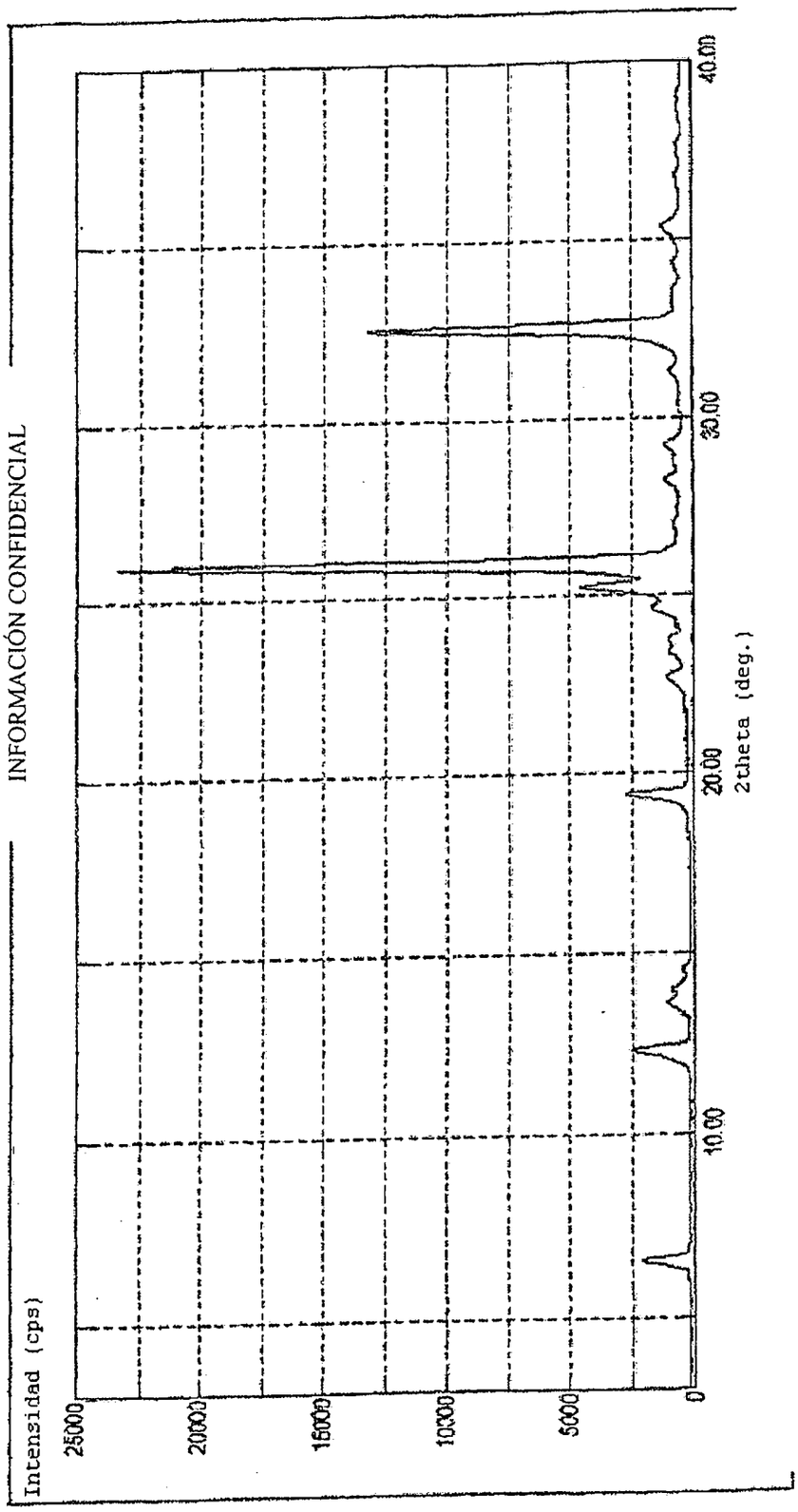
INFORMACIÓN CONFIDENCIAL

FIGURA 59



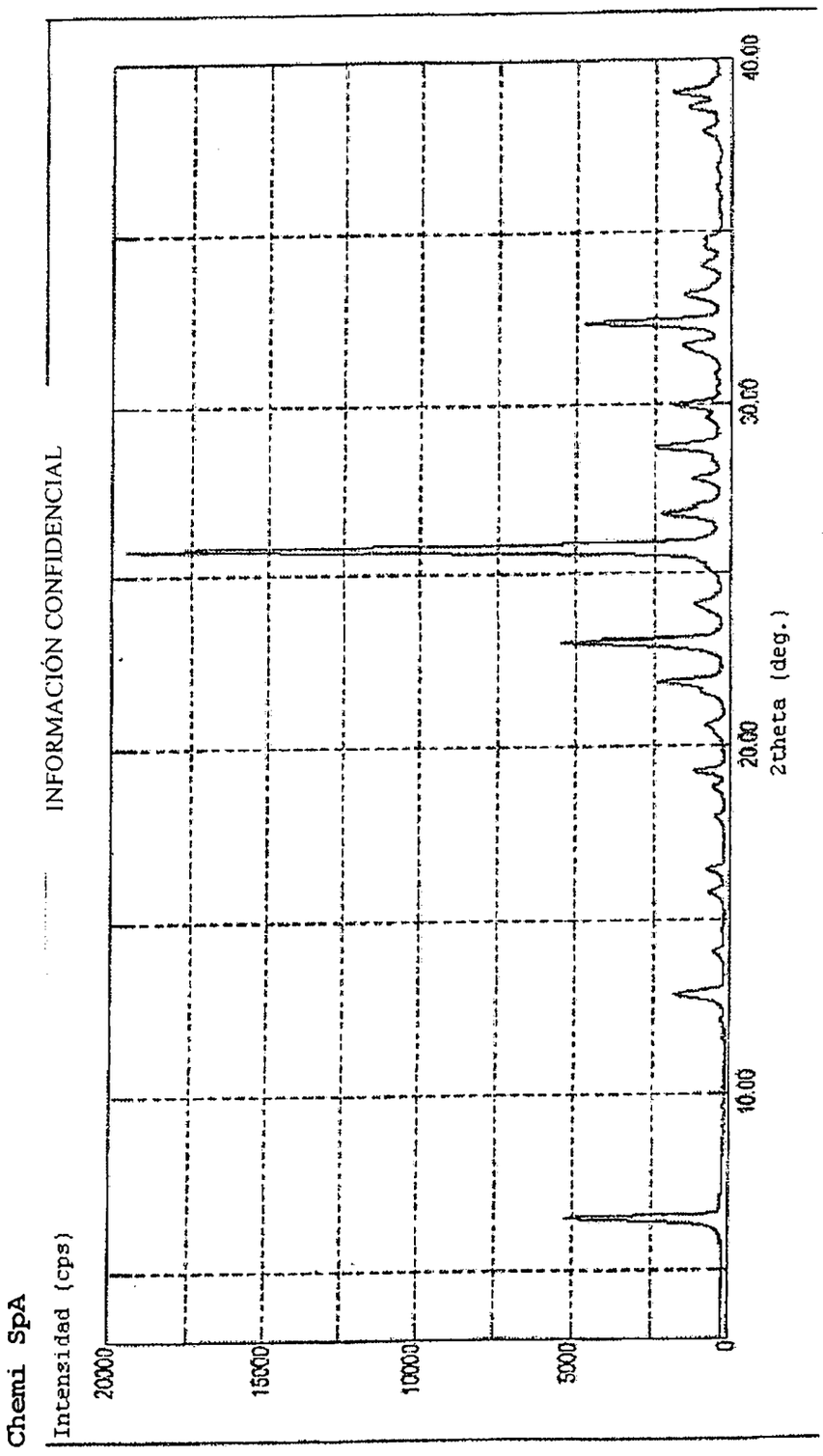
DSC de la forma polimórfica III de Bromhidrato de bupropion

FIGURA 60



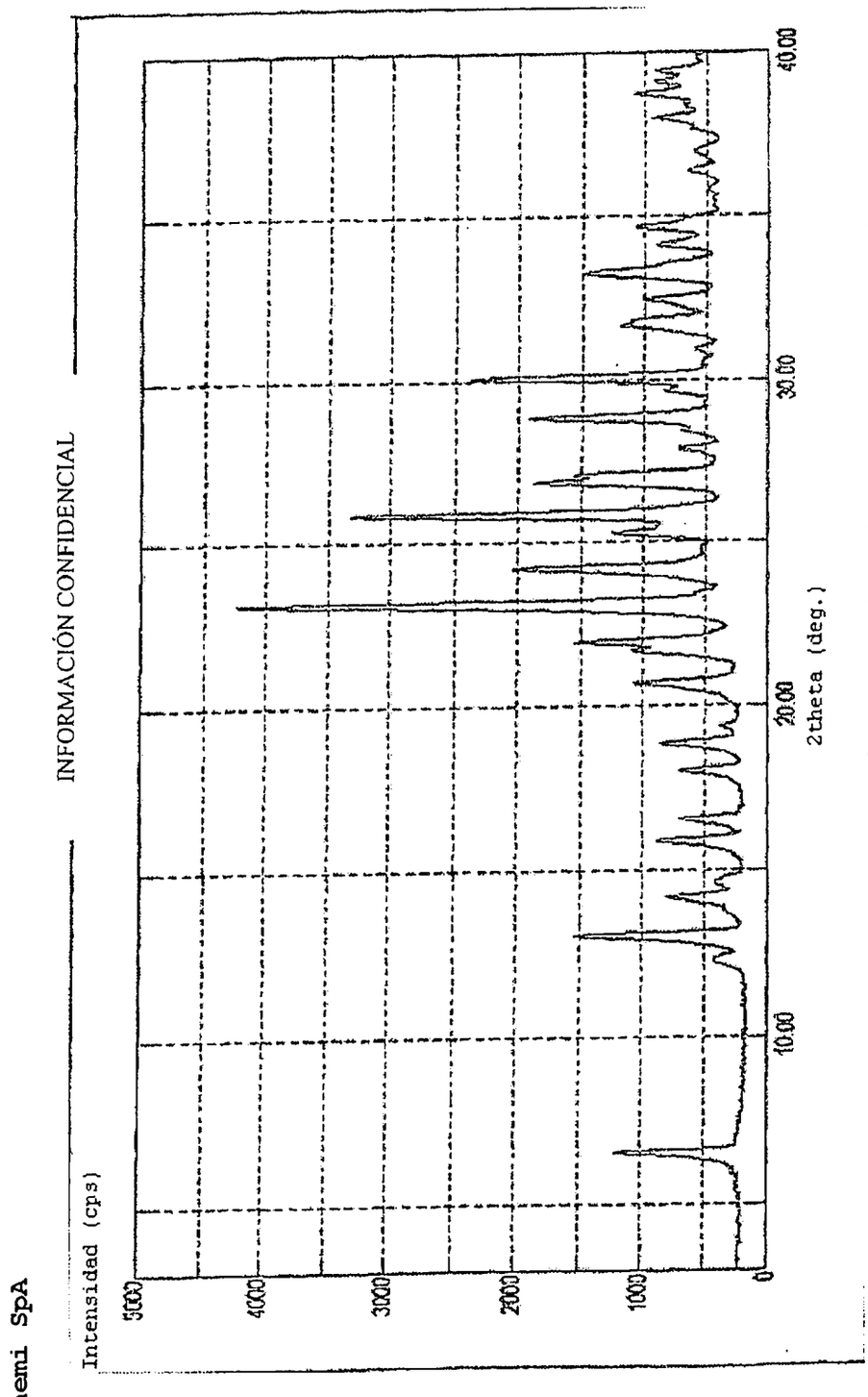
PXRD de la forma polimórfica I de bromhidrato de bupropion después de 6 meses en condiciones ICH (40 °C, 75 % HR)

FIGURA 61



PXRD de la forma polimórfica II de bromhidrato de bupropion después de 1 meses en condiciones ICH (40 °C, 75 % HR)

FIGURA 62



PXRD de la forma polimórfica III de bromhidrato de bupropion después de 1 meses en condiciones ICH (40 °C, 75 % HR)

(HEADER ILLEGIBLE)

"Formulación de una sal de bupropion de liberación modificada"
Inventor: Oberegger, et al.
Figura 63; Hoja 63 de 69
Expediente: 56819.000001; Nº de Cliente 21967

REPORTE DE ESTABILIDAD TEMPORAL

Proyecto: BUP 10121		Producto: **Bupropion HBr XL comprimidos de 348 mg**				Nº de Lote: **Bup-HBr-XL-348-025-5** Fecha de vencimiento: N/A	
Lugar de fabr. del fármaco activo: N/A		Lugar de fabr. del producto: N/A	Lugar de envasdo: N/A	Fecha de envasado: N/A		Nº del Estudio de estabilidad : STAB-05/064	
Fecha de fabr. del fármaco activo: N/A		Fecha de fabr. del producto: N/A	Envase: Frasco	Desecante: N/A		Programa de estabilidad: A largo plazo	
Nº de lote del fármaco activo: N/A		Tamaño del lote del producto: N/A	Cierre: N/A	Unidades: 90 unidades		Condiciones de almacenamiento: 25ºC/60 % de HR	
Fecha de vencimiento del fármaco activo: N/A		Descripción del producto: N/A				Programa: inicial, 3 M, 6 M, 9 M, 12 M	
PRUEBAS Y METODOS	ESPECIFICACIONES	INICIAL		3 MESES	6 MESES	9 MESES	12 MESES
		Fecha: 20 MAY/ 2005		Fecha: 20 AGO/ 2005	Fecha: 20 NOV/ 2005	Fecha: 20 FEB/2006	Fecha: 20 MAY/ 2006
	Nº de muestra de laboratorio	E05-71		H05-35	K05-51	B06-51	
Descripción	Informar resultados	Comprimidos redondos blanco hueso		Cumple	Cumple	Cumple	
Contenido (%)	Informar resultados	99,6		99,4	97,4	96,8	
Impurezas (%)							
-3-CBA	NMD 0,7 %	0,012		0,046	0,071	0,172	
-852U77	NMD 1,0 %	0,028		0,138	0,185	0,207	
-20U78/diluyente	NMD 0,3 %	0,034		0,051	0,040	0,046	
-827U76	NMD 0,4 %	ND		0,011	0,018	0,010	
-Desconocida mayor	Informar resultados	0,253 (RRT 0,14)		0,186 (RRT 0,13)	0,657 (RRT 0,09)	0,177 (RRT 0,15)	
-Desconocidas totales	Informar resultados	0,376		0,342	1,055	0,280	
-Impurezas totales	Informar resultados	0,45		0,59	1,37	0,72	
KF (%)	Informar resultados	0,62		0,85	0,42	0,49	
Disolución*							
2H	NMD 20 %	14-19 (16)		13-17 (15)	12-17 (14)	12-20 (16)	
4H	20-45 %	33-40 (36)		30-35 (32)	29-36 (32)	29-40 (34)	
8H	65-85 %	64-72 (68)		57-64 (61)	54-63 (58)	55-68 (61)	
16H	NMD 80 %	92-101 (98)		91-98 (94)	89-97 (93)	92-100 (96)	
*Especificación tentativa							
Revisado por/fecha:							

Forma AL-050DC.00

REPORTE DE ESTABILIDAD TEMPORAL

Proyecto: BUP 10121	Producto: **Bupropion HBr EA comprimidos de 300 mg**			Nº de Lote: **Bup-HBr-EA-300-001-5** Fecha de vencimiento: N/A	
Lugar de fabr. del fármaco activo: N/A	Lugar de fabr. del producto: N/A	Lugar de envasdo: N/A	Fecha de envasado: N/A	Nº del Estudio de estabilidad : STAB-05/072	
Fecha de fabr. del fármaco activo: N/A	Fecha de fabr. del producto: 19 Abr. 2005	Envase: Frasco	Desecante: N/A	Programa de estabilidad: Acelerada	
Nº de lote del fármaco activo: N/A	Tamaño del lote del producto: N/A	Cierre: N/A	Unidades: 90 unidades	Condiciones de almacenamiento: 40°C/75 % de HR	
Fecha de vencimiento del fármaco activo: N/A	Descripción del producto: Comprimidos recubiertos- 54 mg de aumento de peso			Programa: inicial, 1 M, 2 M, 3 M, 6 M	

PRUEBAS Y METODOS	ESPECIFICACIONES	INICIAL	1 MES	2 MESES	3 MESES	6 MESES
		Fecha: 13 JUN/2005	Fecha: 13 JUL/2005	Fecha: 13 AGO/2005	Fecha: 13 SEP/2005	Fecha: 13 DIC/2005
	Nº de muestra de laboratorio	F05-5	G05-10	H05-24	I05-13	L05-23
Descripción	Informar resultados		Cumple	Cumple	Cumple	
Contenido (%)	Informar resultados	102,3	99,6	98,0 (*)	101,8	101,0
Impurezas (%)						
-3-CBA	NMD 0,7 %	0,017	0,052	0,180	0,170	0,318
-852U77	NMD 1,0 %	0,023	0,221	0,438	0,256	0,221
-20U78/diluyente	NMD 0,3 %	0,044	0,036	0,032	0,057	0,059
-827U76	NMD 0,4 %	0,013	0,043	0,032	0,030	0,037
-Desconocida mayor	Informar resultados	0,623 (RRT 0,10)	0,315 (RRT 0,10)	0,205 (RRT 0,13)	0,245 (RRT 0,14)	0,651 (RRT 0,10)
-Desconocidas totales	Informar resultados	1,054	0,675	0,381	0,421	1,125
-Impurezas totales	Informar resultados	1,15	1,03	1,06	0,93	1,76
KF (%)	Informar resultados	1,02	0,81	1,39	0,79	0,42
Disolución*						
2H	NMD 20 %	13–15 (14)	14-17 (16)	15-17 (16)	14-18 (16)	12-13 (13)
4H	20–45 %	32–35 (33)	33-37 (35)	35-38 (36)	33-38 (35)	28-31 (30)
8H	65-85 %	64–69 (66)	64-69 (67)	65-71 (68)	62-68 (65)	55-59 (57)
16H	NMD 80 %	96–101 (98)	97-100 (98)	97-102 (99)	95-99 (97)	90-92 (91)

*Especificación tentativa

Comentarios: Nota: Los resultados de impureza se calcularon basándose en valores correctos — Revisado por/fecha:

REPORTE DE ESTABILIDAD TEMPORAL

Proyecto: BUP 10121	Producto: **Bupropion HBr EA comprimidos de 300 mg**			N° de Lote: Bup-HBr-EA-300-001-5 Fecha de vencimiento: N/A
Lugar de fabr. del fármaco activo: N/A	Lugar de fabr. del producto: N/A	Lugar de envasdo: N/A	Fecha de envasado: N/A	N° del Estudio de estabilidad : STAB-05/072
Fecha de fabr. del fármaco activo: N/A	Fecha de fabr. del producto: 19 Abr/2005	Envase: Frasco	Desecante: N/A	Programa de estabilidad: Acelerado
N° de lote del fármaco activo: N/A	Tamaño del lote del producto: N/A	Cierre: N/A	Unidades: 90 unidades	Condiciones de almacenamiento: 40°C/75 % de HR
Fecha de vencimiento del fármaco activo: N/A	Descripción del producto: Comprimidos recubiertos-54 mg de aumento de peso			Schedule: inicial, 1M, 2M, 3M, 6M
				Aprobado por/fecha:

Bupropion HBr XL núcleo de 174 mg. N° Lote Bup-HBr-XL-004-5 núcleo

Pruebas	Inicial	Estabilidad en frasco abierto-cerrado (40 °C/75 % de H.R.)			
		10 días-Abierto	10 días-Cerrado	20 días-Abierto	20 días-Cerrado
Contenido %	100,1	98,7	98,2	99,2	97,6
% Impurezas 3-CBZ	0,010	0,179	0,184	0,276	0,465
852U77	0,019	0,209	0,268	0,248	0,416
20U78/dilu	0,054	0,055	0,060	0,058	0,063
827U76	0,026	0,131	0,308	0,102	0,497
Desconocidas totales	0,054	0,043	0,075	0,042	0,038
Total	**0,16**	**0,62**	**0,89**	**0,73**	**1,48**

Bupropion HBr XL núcleo de 348 mg. N° Lote Bup-HBr-XL-009-5 núcleo

Pruebas	Inicial	Estabilidad en frasco abierto-cerrado (40°C/75 % HR)			
		10 días-Abierto	10 días-Cerrado	20 días-Abierto	20 días-Cerrado
Contenido %	98,3	97,8	95,6	96,9	98,0
% Impurezas 3-CBZ	0,016	0,106	0,121	0,146	0,166
852U77	0,091	0,391	0,411	0,414	0,483
20U78/dilu	0,054	0,051	0,055	0,056	0,055
827U76	0,020	0,077	0,102	0,059	0,119
Desconocidas totales	0,053	0,126	0,156	0,124	0,142
Total	**0,23**	**0,74**	**0,84**	**0,80**	**0,97**

Bupropion HCl XL núcleo de 150 mg. N° Lote 05E056

Pruebas	Inicial	Estabilidad em frasco abierto-cerrado (40°C/75 % HR)			
		10 días-Abierto	10 días-Cerrado	20 días-Abierto	20 días-Cerrado
Contenido %	97,5	98,4	97,5	98,1	97,6
% Impurezas 3-CBZ	0,006	0,079	0,052	0,185	0,238
852U77	0,043	0,406	0,342	0,520	0,685
20U78/dilu	0,044	0,046	0,046	0,059	0,052
827U76	0,028	0,050	0,074	0,069	0,127
Desconocidas totales	0,058	0,051	0,066	0,044	0,400
Total	**0,18**	**0,63**	**0,58**	**0,88**	**1,14**

Bupropion HCl XL núcleo de 300 mg. N° Lote 05D380

Pruebas	Inicial	Estabilidad en frasco abierto-cerrado (40°C/75 % HR)			
		10 días abierto	10 días cerrado	20 días abierto	20 días cerrado
Contenido %	99.2	99,1	98,4	96,8	97,1
% Impurezas 3-CBZ	0,006	0,100	0,016	0,245	0,171
852U77	0,037	0,409	0,274	0,564	0,515
20U78/dilu	0,044	0,045	0,046	0,051	0,050
827U76	0,015	0,058	0,039	0,099	0,105
Desconocidas totales	0,044	0,038	0,045	0,032	0,052
Total	**0,15**	**0,65**	**0,42**	**0,99**	**0,90**

Estudio 2B, estabilidad, núcleos Bup-HBr-XL174-150-300-348

Comprimidos de bupropion HBr XL de 348 mg (finales) N° Lote Bup-HBr-XL-012-5 (USP3)

Medio/Tiempos de muestreos		Recipiente 1	Recipiente 2	Recipiente 3	Recipiente 4	Recipiente 5	Recipiente 6	Media
LGS pH 1,2	2 hs	9,0	8,3	8,9	11,6	8,8	8,6	**9,2**
Sol. amortiguadora de acetato de pH 4,5	2 hs	15,8	15,0	19,3	18,5	17,5	18,2	**17,4**
Sol. amortiguadora de fosfato de pH 6,8	2 hs	26,8	25,4	24,9	33,3	27,7	24,2	**27,1**
	2 hs	24,2	15,5	24,8	31,9	37,8	15,3	**24,9**
	2 hs	22,5	19,5	16,6	1,4	2,4	25,8	**14,7**
	6 hs	1,0	11,6	0,8	0,2	0,2	6,1	**3,3**
Total liberado %		99,3	95,3	95,3	96,9	94,4	98,2	**96,6**

Comprimidos de Wellbutrin XL de 300 mg (finales)-N°Lote 05A116 (USP3)

Medio/Tiempos de muestreos		Recipiente 1	Recipiente 2	Recipiente 3	Recipiente 4	Recipiente 5	Recipiente 6	Media
LGS pH 1,2	2 hs	3,1	2,7	2,1	1,8	2,8	2,6	**2,5**
Sol. amortiguadora de acetato de pH 4,5	2 hs	53,0	38,8	32,6	10,7	20,1	38,8	**32,3**
Sol. amortiguadora de fosfato de pH 6,8	2 hs	30,8	36,4	37,0	47,8	46,1	33,5	**38,6**
	2 hs	5,6	15,2	25,0	22,4	22,8	19,6	**18,4**
	2 hs	2,2	3,1	1,6	13,7	2,8	0,8	**4,0**
	6 hs	0,9	0,3	0,2	0,9	0,2	0,1	**0,4**
Total liberado %		95,7	96,3	98,4	97,3	94,8	95,2	**96,3**

Comprimidos de bupropion HBr XL de 348 mg (ECI) N° Lote Bup-HBr-XL-012-5 (EC 32 mg aumento de peso) (USP3)

Medio/Tiempos de muestreos		Recipiente 1	Recipiente 2	Recipiente 3	Recipiente 4	Recipiente 5	Recipiente 6	Media
LGS pH 1,2	2 hs	47,6	45,7	45,0	51,3	42,7	48,0	**46,7**
Sol. amortiguadora de acetato de pH 4,5	2 hs	38,0	37,9	37,3	37,9	36,0	38,0	**37,5**
Sol. amortiguadora de fosfato de pH 6,8	2 hs	13,0	13,9	16,0	10,3	15,8	12,3	**13,5**
	2 hs	1,9	2,1	3,1	0,9	3,5	1,5	**2,2**
	2 hs	0,4	0,5	0,9	0,2	1,0	0,3	**0,6**
	6 hs	0,2	0,2	0,4	0,1	0,4	0,1	**0,2**
Total liberado %		100,9	100,3	102,7	100,6	99,4	100,2	**100,7**

Comprimidos de Wellbutrin XL de 300 mg (ECI)-N°Lote 05D047 (USP3)

Medio/Tiempos de muestreos		Recipiente 1	Recipiente 2	Recipiente 3	Recipiente 4	Recipiente 5	Recipiente 6	Media
LGS pH 1,2	2 hs	63,1	61,5	58,9	58,2	57,9	60,8	**60,1**
Sol, amortiguadora d acetato de pH 4,5	2 hs	32,9	35,4	36,6	38,2	37,2	35,3	**35,9**
Sol. amortiguadora de fosfato de pH 6,8	2 hs	0,6	0,9	1,0	1,0	1,1	0,9	**0,9**
	2 hs	0,0	0,1	0,1	0,1	0,1	0,1	**0,1**
	2 hs	0,0	0,0	0,0	0,0	0,0	0,0	**0,0**
	6 hs	0,0	0,1	0,1	0,0	0,1	0,0	**0,0**
Total liberado %		96,7	97,9	96,6	97,6	96,3	97,1	**97,0**

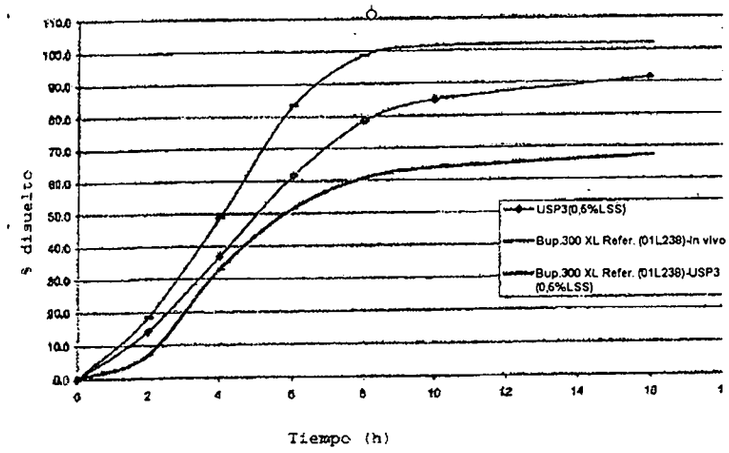
Bup HBr-348mg-WXL 300-recubrimiento de EC y final-UPS-3

Diferentes medios USP-3 (LGS pH 1,2+0,5 % LSS, Sol. Amort de acetato de pH 4,5 y Sol. Amort de fosfato de pH 6,8) Bupropion HBr 348 mg Lote 05E304

Medio/Tiempos de muestreos		Recipiente 1	Recipiente 2	Recipiente 3	Recipiente 4	Recipiente 5	Recipiente 6	Media
LGS pH 1,2+0,5% LSS	2 hs	14,5	14,6	12,5	14,9	13,3	16,3	14,3
Sol. amortiguadora de acetato de pH 4,5	2 hs	23,2	21,7	19,6	23,1	22,2	26,0	22,6
Sol. amortiguadora de fosfato de pH 6,8	2 hs	26,1	25,1	23,9	24,7	25,3	23,6	24,8
	2 hs	16,1	20,7	16,5	14,3	16,7	16,3	16,8
	2 hs	12,9	15,2	9,4	10,2	10,4	10,6	11,4
	6 hs	2,5	1,1	2,6	14,4	11,3	6,8	6,4
Total liberado %		95,3	98,2	84,5	101,6	99,1	99,5	96,4

Tiempo (h)	USP3(0,5 % LSS)	Bup 300 XL Refer. (01L238 In vivo	Bup 300 XL Refer. (01L238)-USP3(0,5 % LSS)
0	0,0	0,0	0,0
2	14,3	7,1	18,5
4	36,9	33,0	48,8
6	61,7	51,5	83,4
8	78,5	60,8	98,9
10	84,9	63,8	101,5
16	91,3	67,2	101,9

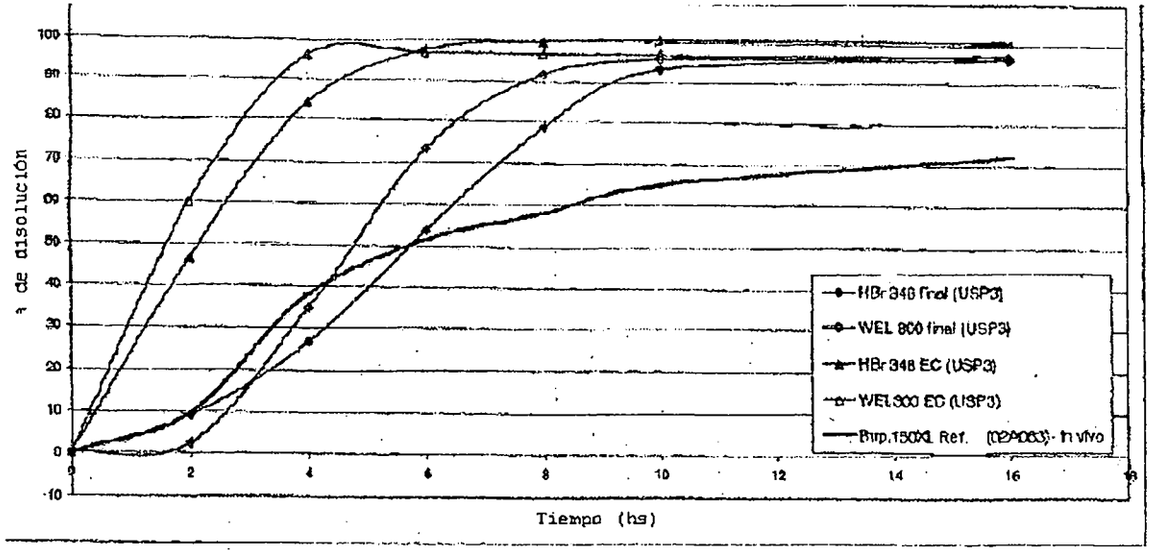
Bupropion HBr 348 mg, lote 05E304 (USP3) vs Bup HCl XL 300 mg in vivo (también USP3-0,5 % LSS)



Datos acumulados
LGS-(UPS-3) de pH 1.2, solución amortiguadora de acetato de pH 4.5, solución amortiguadora de fosfato de pH 6.8

Tiempo (hs)	HBr 348 final (USP3)	WEL 300 final (USP3)	HBr 348 EC (USP3)	WEL300 EC (USP3)	Bup.150 XL Refer. (02A063) in vivo
0	0.0	0.0	0.0	0.0	0.0
2	9.2	2.5	46.7	60.1	9.7
4	28.6	34.8	84.2	96.0	38.1
6	53.7	73.4	97.7	96.9	51.5
8	78.8	91.8	99.9	97.0	58.0
10	93.3	95.8	100.5	97.0	65.0
16	96.6	96.2	100.7	97.0	72.3

Datos acumulados de perfiles comparativos de comprimidos de Bupropion HBr XL 348 mg y Wellbutrin XL (final y EC) en diferentes medios USP-3 (LGS, sol amort. de acetato y pH 6,8) vs. datos in vivo de Bupropion HCl XL 150 mg referencia (02A063)



Bup - HBr - 348 mg - WXL - recubrimiento de EC y final - VSP-3

951

PATENT COOPERATION TREATY PCT/US2006/024832

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

TREANOR, Richard, L.
Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
1940 Duke Street
Alexandria, VA 22314
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)*
30 October 2007 (30.10.2007)

Applicant's or agent's file reference
56819.01-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/US2006/024832

International filing date *(day/month/year)*
27 June 2006 (27.06.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

State of Nationality | State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
SALEH, Mohammad, Ashty
223 Gatwick Drive
Oakville, Ontario,L6H 6T6
Canada

State of Nationality: CA | State of Residence: CA

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:
The person identified in Box 2 should be added to the record as an inventor for all designated States and an applicant for the United States of America only. This request for the recording of a change according to PCT Rule 92bis was received by the International Bureau between 20 and 30 months from the priority date.

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 70 80

Authorized officer
Deprez Isabelle
e-mail pt11.pct@wipo.int
Telephone No. +41 22 338 74 11

Form PCT/IB/306 (October 2005) I/DFR5RE6C0

FIGURA 1

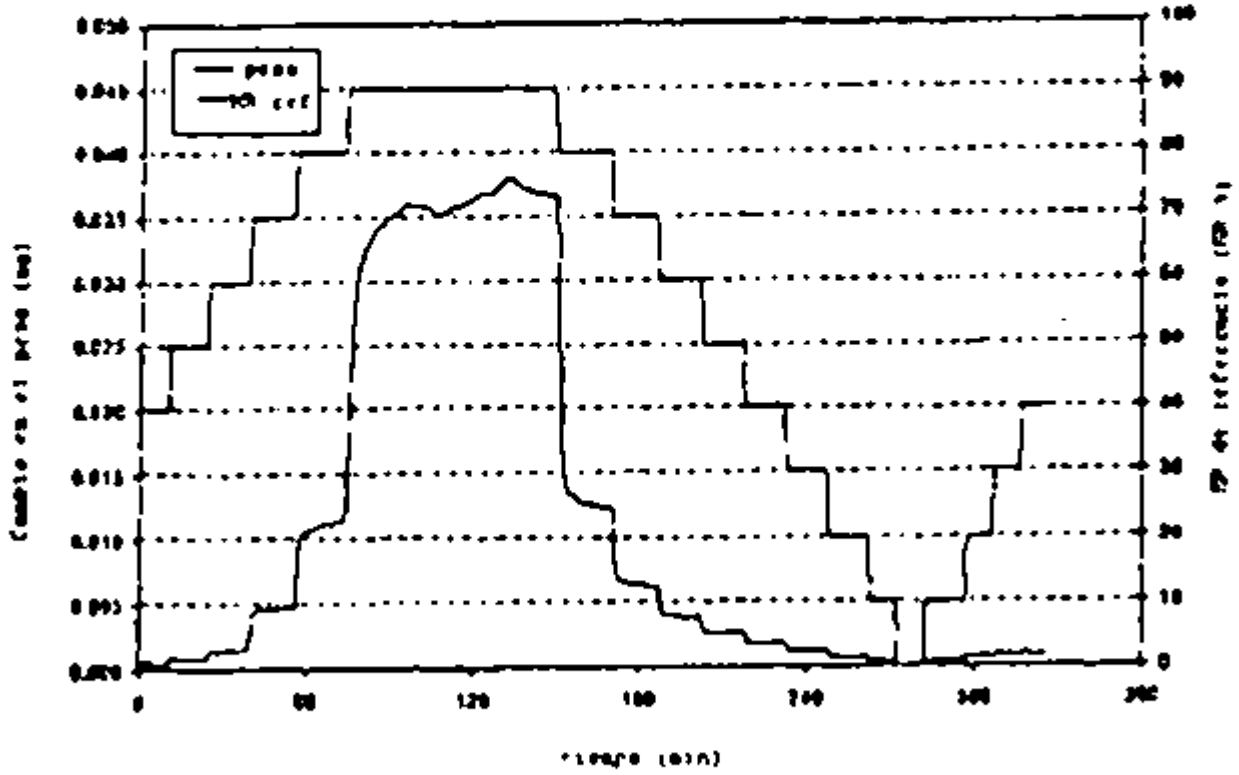
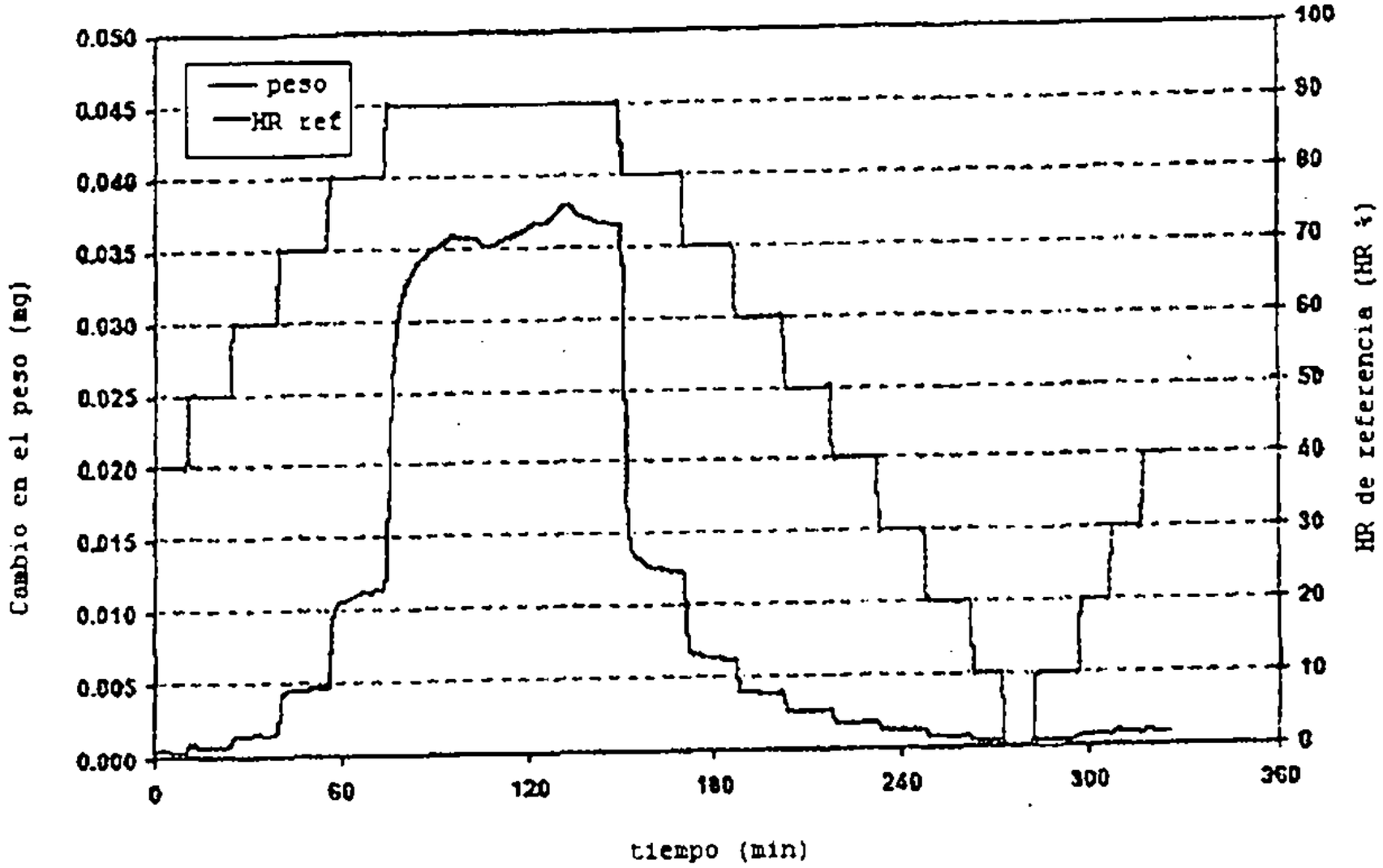


FIGURA 1


peso
HR ref
0.050
0.045
0.040
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
Cambio en el peso (mg)
100
90
80
70
60
50
40
30
20
10
0
HR de referencia (HR %)
0
60
120
180
240
300
360
tiempo (min)

954

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO OFICIAL DE CAJA : 07 - 100,353
FECHA : DICIEMBRE 10 DE 2007

No. 07-136836- -00000-0000

Fecha: 2007-12-27 18:12:00 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 954

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	49377610	10/12/2007	44,065,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo 15439 - 841-002-2

955

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-136836- -00000-0000

Fecha: 2007-12-27 18:12:00 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 954

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- ◆ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- ◆ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edgar Narcono

Firma Responsable

Fecha 27-12-07

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