

No. 10-011409-00003-0000

Fecha: 2011-05-17 15:21:38 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 35

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A :

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Número del expediente: 10 - 011.409
Solicitante: BIOVAIL LABORATORIES INTERNATIONAL SRL
Apoderado: LUZ CLEMENCIA SUAREZ DE PAEZ
Título de la nueva creación o denominación del signo: "BROMHIDRATO
DE BUPROPION Y APLICACIONES TERAPEUTICAS"
Gaceta: 625

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: LABORATORIOS SYNTHESIS S.A.S.	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>860.000.760-1</u>
	Dirección: Carrera 44 N° 20 C 73 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BOGOTA Teléfono: 3692222 Fax: 3693542 E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: ELINA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>51.975.664</u> TP <u>83823</u>
	Dirección: CARRERA 104 N°119-95 OF 104 Teléfono: 2131213 Fax: 6121979 E-mail: negocios@optimum-co.com	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: _____

Eliana I Moreno B

FIRMA: _____

Eliana I Moreno B

C.C. 51.975.664

TP. 83823

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 10 011.409

Asunto : Oposición a la solicitud de patente de Invención titulada
"BROMHIDRATO DE BUPROPION Y APLICACIONES
TERAPÉUTICAS"

Solicitante : BIOVAIL LABORATORIES INTERNATIONAL SRL

Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 625 del 21 de febrero de 2011

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "BROMHIDRATO DE BUPROPION Y APLICACIONES TERAPEUTICAS", cuyo titular es **BIOVAIL LABORATORIES INTERNATIONAL SRL**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **BUPRONION**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 3 de FEBRERO de 2010, reivindicando prioridad bajo la solicitud US20070834848 del 2007-08-07; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° **625 del 21 de febrero de 2011**, cuya publicación internacional corresponde a la WO 2009019294 del 2009-02-12.

2.2. La solicitud colombiana **10 011.409** objeto de la presente oposición, se refiere a 1.- Una composición que comprende bromhidrato de bupropion y al menos un excipiente farmacéuticamente aceptable; en donde la administración de una cantidad de un bromhidrato de bupropion a una primera rata resulta en menos incidencias de crisis convulsivas inducidas por bupropion y/o crisis convulsivas inducidas por bupropion menos graves en comparación con las incidencias y/o

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

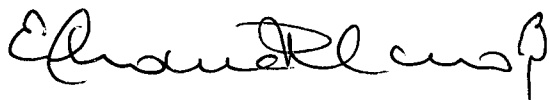
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS
SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US 2007027213 publicada el 1 de febrero de 2007.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

PODER ESPECIAL

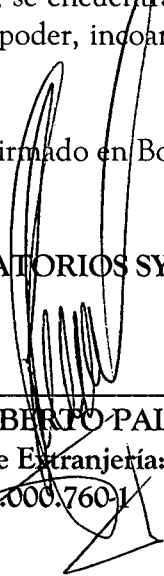
Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Gerente de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 0 011.409, titulada "**BROMHIDRATO DE BUPROPION Y APLICACIONES TERAPÉUTICAS**", cuyo titular es **BIOVAIL LABORATORIES INTERNATIONAL SRL**, publicada en la gaceta No. 625 del 21 de febrero de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

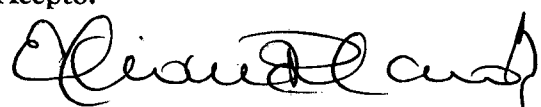
Dado y Firmado en Bogotá (Colombia) a los 05 días del mes de Mayo de 2011.

LABORATORIOS SYNTHESIS S.A.S.

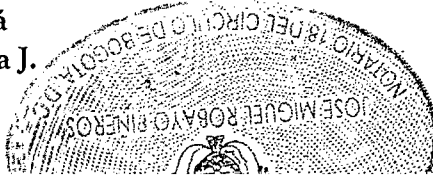


LUIS ALBERTO PALACIOS
Cédula de Extranjería: No. 319788.
NIT: 860.000.760-1
Gerente

Acepto:



ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.





DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Bogotá.

DALACIES **ALBERTO**
quien exhibió la C. **319788**

Expedida en **EST** y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

6 MAY 2011

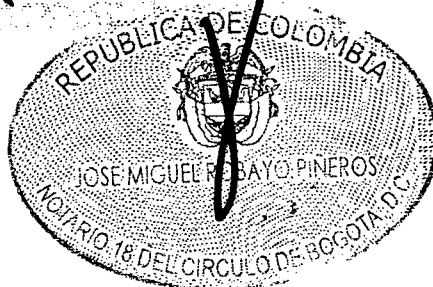
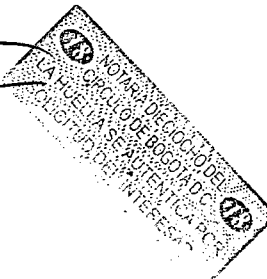
BOGOTÁ, D.C.

[Signature]
FIRMA



HUELLA DEL
INDICE DERECHO

EL NOTARIO



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0045367

Bogotá D.C., Mayo 12 de 2011 - 10:25:29

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.

NI 860.000.760

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	382600083	10/05/2011	912.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12	MARCAS Y LEMAS COMERCIALES
			304.000.00	304.000.00
				\$304.000.00

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



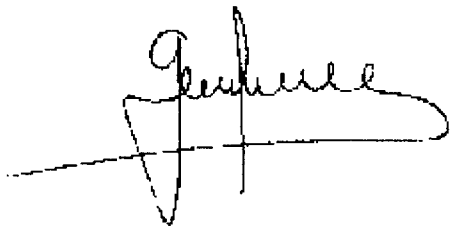
N 1409-00003-0000
Fecha: 2011-05-17 15:21:38 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 35

~~RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU~~
EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : \$ 3,700

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA
POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO
DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

A handwritten signature in black ink, appearing to be 'García', written over a horizontal line.

Anexo 1



US 20070027213A1

(19) **United States**

(12) **Patent Application Publication**
Oberegger et al.

(10) **Pub. No.: US 2007/0027213 A1**

(43) **Pub. Date: Feb. 1, 2007**

(54) **MODIFIED RELEASE FORMULATIONS OF
A BUPROPION SALT**

(22) Filed: **Jun. 27, 2006**

Related U.S. Application Data

(75) Inventors: **Werner Oberegger**, Mississauga (CA);
Fang Zhou, Centreville, VA (US); **Paul
Maes**, Toronto (CA); **Stefano
Turchetta**, Rome (IT); **Graham
Jackson**, Celbridge (IE); **Pietro
Massardo**, Rome (IT); **Mohammad
Ashty**, Oakville (CA)

(60) Provisional application No. 60/693,906, filed on Jun.
27, 2005.

Publication Classification

(51) **Int. Cl.**
A61K 31/195 (2006.01)

(52) **U.S. Cl.** **514/563**

Correspondence Address:

HUNTON & WILLIAMS LLP
INTELLECTUAL PROPERTY DEPARTMENT
1900 K STREET, N.W.
SUITE 1200
WASHINGTON, DC 20006-1109 (US)

(57) **ABSTRACT**

(73) Assignee: **Biovail Laboratories International
S.R.L.**, Mississauga (CA)

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.

(21) Appl. No.: **11/475,252**

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.

[0593] 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 different time periods.

[0594] 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.

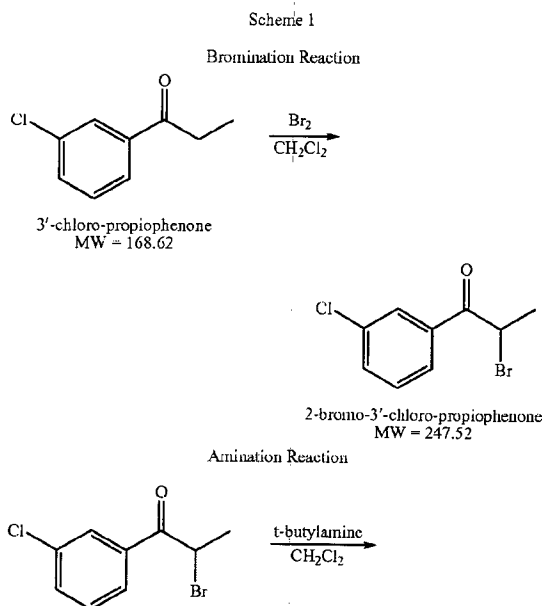
[0595] The following examples illustrate the present invention and are not intended to limit the scope of the present invention.

EXAMPLES

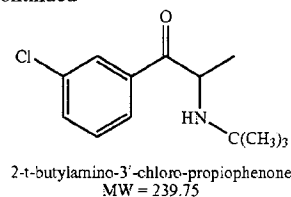
Example 1

Preparation of Bupropion HBr Salt

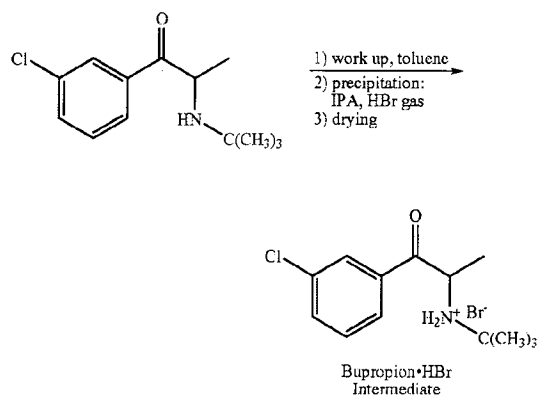
[0596] Bupropion HBr salt was prepared according to the method shown in Scheme 1:



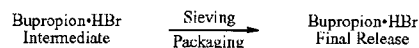
-continued



Work Up/Precipitation/Drying



Finishing Step



(a) Bromination and Condensation Reactions

[0597] 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.

[0598] 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.

[0599] 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

Physicochemical Characterization of Bupropion Salts

[0600] The following bupropion salts were characterized against the HCl salt:

Product ID	Lot#	Quantity	Potency (HPLC) determined by R&D
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:

[0601] 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:

[0602] 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%.

[0603] The salts were analysed by DSC (at 10° C./min from 30° C. up to 400° C.) 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.

[0604] Maleate: DSC showed a melting endothermic peak at the onset temperature 199.1° C. and a smaller sharp peak at 205° C. The moisture content was 0.10% and the pH of the aqueous solution of 0.5% was 4.29.

[0605] 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 150° C. as 1.3% weight lost between room temperature and 100° C. was observed. Like Bupropion HCl, no glass transition was observed when a heat-cool-heat experiment was done by TA instrument.

[0606] Fumarate: DSC showed multiple endothermic peaks at different onset temperatures (172.3, 182.3, 202 and 217° C.). The moisture content was 0.09% and the pH of the aqueous solution of 0.5% was 3.84.

[0607] Tosylate: DSC showed a melting endothermic peak at the onset temperature 150° C., a smaller peak at 90° C. and multiple peaks at higher temperature (>200° C., probably decomposition). The peak at 90° C. 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.

[0608] By re-crystallization in acetonitrile/hexane or acetonitrile/EtOAc, the small peak at 90° C. 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).

[0609] The TGA showed that this product was not thermally stable as 1.3% weight lost was observed between room temperature and 100° C. Also the sample gave a residue of 10.3% at 400° C. as compared to minimal residues for bupropion HCl and maleate. The Heat-Cool-Heat experiment was done by TA instrument showed a glass transition (T_g) at 45° C. The T_g indicates that the morphology is amorphous rather than crystalline.

[0610] HBr: DSC showed melting endothermic peak at temperature 224° C., with a shoulder peak. The sample was run at different temperature rates, 1, 10, 15 & 20° C./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 ~224° C. was observed (i.e. still the same shoulder at 10° C. or higher rates). A Heat-Cool-Heat experiment was done by TA instrument showed a glass transition (T_g) at 23° C.

[0611] The moisture content was 0.00% and the pH of the aqueous solution of 0.5% was 5.92.

[0612] 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.

[0613] A comparison of the solubility & other physical properties of bupropion HBr vs bupropion HCl is presented in Table 3.

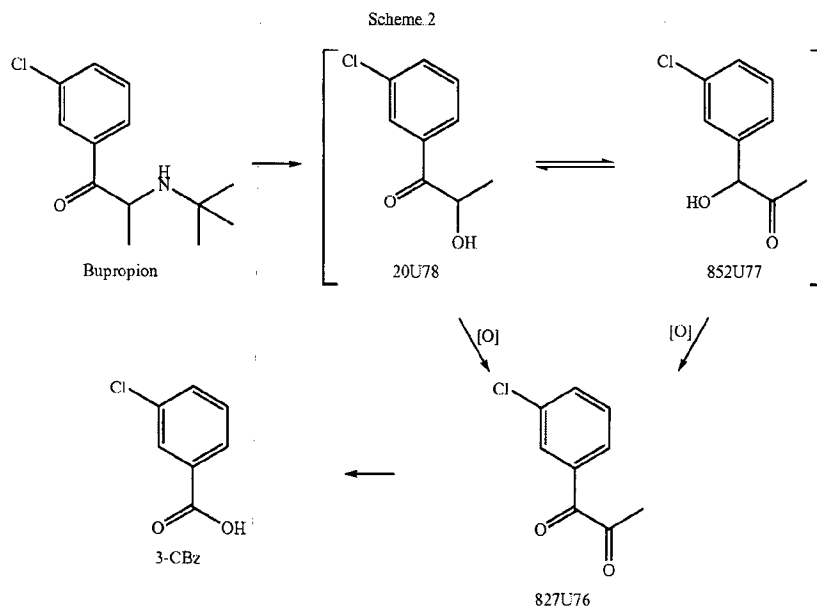
[0614] Hygroscopicity of Bupropion HBr:

[0615] 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 FIG. 1 and DVS isotherm data for bupropion HBr is shown in FIG. 2.

Example 3

Forced Degradation Stability Study

[0616] 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.



[0617] As mentioned above, the stability samples were prepared in 2 mL vials and used directly for assay and impurity analysis by HPLC without further sample preparations to minimize errors.

[0618] 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.

[0619] 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 FIGS. 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 FIGS. 3 and 4. FIGS. 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.

[0620] 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 FIG. 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 (FIG. 4). In the assay study, the order of stability for the bupropion salts was as follows: HBr>HCl>tosylate>fumarate>maleate).

[0621] The stability of the salts was then evaluated under more aggressive conditions. The drug salts (DS) and excipi-

ents were spiked with water, water plus EtOH and IPA and EtOH and IPA. As can be seen from the results shown in FIGS. 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

[0622] 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.

[0623] 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.

[0624] 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 (FIGS. 8-10):

In water,

[0625] 3-CBZ: HCl>HBr≈maleate≈fumarate

[0626] 852U77: fumarate>HBr>maleate>HCl

[0627] Total imp. fumarate>HBr>HCl>tosylate>maleate

In IPA/EtOH:

[0628] 3-CBZ: maleate>HBr>HCl>Fumarate

[0629] 852U77: fumarate>HBr≈HCl≈maleate≈tosylate

[0630] Total imp. fumarate>maleate>HBr>HCl>tosylate

[0631] 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.

[0632] 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.

[0633] 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

[0634] The stability of bupropion HCl and bupropion HBr API salts were further evaluated under the accelerated conditions of 40° C./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.

[0635] 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 40° C./75% RH. The samples were analysed after 14 and 24 days (study-I) 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).

[0636] 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.

[0637] 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.

Example 5

Bupropion HBr Extended Release (XL) Tablets

[0638] The aim of this example was to describe the development of bupropion HBr XL (174 and 348 mg). Granulation, tableting 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.

[0639] 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.

[0640] It was previously observed that when 150 mg of bupropion HCl was tested for its release of bupropion, the base value that was released was 130 mg. However, when 150 mg of bupropion HBr was tested, the base value released was only 112 mg. Thus, the amount of bupropion HBr had to be increased in order to increase the base value from 112 mg to 130 mg, which was the target. Studies showed that 174 mg of bupropion HBr gave a base value release of 130 mg and is therefore why 174 mg was used as opposed to 150 mg bupropion HBr.

[0641] Bupropion HBr XL—Granulation Process

[0642] A summary of the manufacturing process used for the preparation of bupropion HBr XL tablets is shown in FIG. 11.

[0643] 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.

[0644] 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.

[0645] The PVA was dissolved into the purified water using a magnetic stirrer and a clear colourless solution was made.

[0646] The NIRO Fluid Bed was used to granulate the bupropion HBr Granules with the PVA solution in a process known as wet massing. FIG. 12 shows a summary of the granulation procedure.

[0647] 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.

[0648] 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.

[0649] Upon completion of each batch part's granulation, the five parts were combined together. They were hand screened using Mesh No. 14 (1.4 mm) and any oversized granulation was passed through the Comil fitted with a 2 mm screen.

[0650] 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—Tableting Process

[0651] The Beta Press was used to compress the Bupropion HBr tablets. Depending on the dose of the tablet, 174 mg or 348 mg, different tooling sets were used. The 7 mm punches were used to compress the 174 mg tablets and 9 mm and 10 mm punches were used to compress the 348 mg tablets. Tooling was polished prior to each run.

[0652] The tablet weights were determined as being 185.6 mg for the 174 mg dose tablets and 371.2 mg for the 348 mg 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 $\pm 5\%$, and the average tablet weight had a control limit of $\pm 3\%$ (using ten tablets).

[0653] 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 174 mg and 348 mg tablets.

[0654] Friability was determined using tablets that equaled a weight of 6.5 g 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.

[0655] 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.

[0656] Table 12 summarizes the specifications that were kept constant throughout the compression of all the batches.

[0657] The flow chart shown in FIG. 12 describes the steps that led up to and including the tableting process. FIG. 13 shows a summary of the tableting procedure.

Bupropion HBr XL—Coating Process

[0658] A summary of the coating process used for the coating of the Bupropion HBr XL tablets is shown in FIG. 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.

[0659] 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.

[0660] 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.

[0661] 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).

[0662] 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).

[0663] 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).

[0664] Two Final coating solutions were developed and used to coat the Bupropion HBr tablets after they had been first coated with the Ethocel coat.

[0665] One of the following formulations shown in Table 14 was used to coat the tablets with a final coat.

[0666] 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.

[0667] 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.

[0668] Table 15 summarizes the specifications that were monitored in the Ethocel coating process and their ranges.

[0669] Table 16 summarizes the specifications that were monitored in the final coating process and their ranges.

[0670] In-Vitro Studies on the Bupropion HBr Cores

[0671] 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 900 mL of 0.1N HCl and at a speed of 75 rpm. 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.

[0672] 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 900 mL of Simulated Gastric Fluid (SGF) at pH 1.2 with 0.5% of Sodium Lauryl Sulfate (SLS), followed by 2 hours in 900 mL of Acetate Buffer at a pH of 4.5, followed by 12 hours in 900 mL 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

[0673] 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 348 mg tablets using the Beta press with 9 mm and 10 mm standard, round, concave tooling. Table 17 describes the amounts of each material in the granulation of the 348 mg

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 (FIG. 15). Dissolution was conducted on the 348 mg cores in order to determine their release (FIG. 16).

[0674] 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 9 mm and 10 mm tooling, respectively.

[0675] 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.

[0676] Tablets with a hardness of 4 kp, 6-7 kp and 9-10 kp were compressed and the dissolution profiles of each were shown in FIG. 15. It was observed that there was no significant difference between the three different hardness ranges.

[0677] The dissolution profiles of the 348 mg (FIG. 16) and 174 mg cores (FIG. 17) showed that the cores were releasing approximately 100 percent of API in an hour.

[0678] Dissolution of the 10 mm, 348 mg cores was done also in order to see if these tablets released faster when compared to the 9 mm cores due to their larger surface area (FIG. 17).

[0679] When the dissolution results of the 9 mm and 10 mm cores were compared (FIG. 18), the 10 mm cores showed no difference from the 9 mm cores. Thus, the 10 mm cores were no longer manufactured or used in this study.

Study on Batch BUP-HBr-XL-021-5

[0680] The Formulation was granulated using NIRO Fluid Bed. The final blend was compressed into 174 mg tablets using the Beta press with 7 mm standard, round, concave, stainless steel tooling. Table 20 describes the amounts of each material in the granulation of the 174 mg tablets. It was noted that the 348 and the 174 mg 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 174 mg cores in order to see their release (FIG. 19).

[0681] 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 7 mm tooling.

[0682] The dissolution profile of the 174 mg (FIG. 19) showed that the cores were releasing approximately 100 percent of API in an hour.

Study on Batch BUP-HBr-XL-348 mg-013-5

[0683] Using 348 mg tablets, an Ethocel coating followed by a Final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0684] 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.

[0685] 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.

[0686] It took 2 hours and 25 minutes to coat the tablets with a weight gain of 32 mg. Tablet weights were taken and recorded in Table 23 at 28 mg, 30 mg, 32 mg, and 34 mg weight gains.

[0687] The dissolution profile (FIG. 20) shows that the tablets with the 34 mg weight gain of EC coating released Bupropion HBr the slowest when compared to the others and that the tablets with the 28 mg weight gain released Bupropion HBr the fastest when compared to the other weight gains.

[0688] 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.

[0689] 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.

[0690] 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.

[0691] It took 31 minutes to add a 7 mg weight gain of the final coating solution to the tablets.

[0692] Tablet weights were taken and recorded in Table 25 at 4 mg, 5 mg, 6 mg and 7 mg weight gains.

[0693] The dissolution profile (FIG. 21) shows that the tablets with the 7 mg weight gain of Final coating released the slowest when compared to the other two weight gains (5 mg and 6 mg weight gains).

Study on Batch BUP-HBr-XL-348 mg-018-5

[0694] Using 348 mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0695] 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.

[0696] 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.

[0697] The coating process of this trial took 2 hours and 13 minutes to obtain a 32 mg weight gain. Tablet weights were taken and recorded in Table 27 at 26 mg, 28 mg, 30 mg, and 32 mg weight gains.

[0698] FIG. 22 shows that the tablets with the 30 mg and 32 mg weight gain of EC coating solution released at almost

the same rate. The tablets with the 32 mg weight gain released slower than the tablets with the 30 mg weight gain in the first 5 hours of dissolution. After 6 hours, the tablets with the 32 mg weight gain released slightly faster than those with a 30 mg weight gain. The f_2 similarity factor confirmed that the release rate of both weight gains was similar (91.32%).

[0699] 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.

[0700] The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40° C.; Product Temperature: 35° C. $\pm$ 5° C.; and Supply Air Flow: 200 CFW.

[0701] It took 41 minutes to add a 7 mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded in Table 29 at 4 mg, 5 mg, 6 mg, and 7 mg weight gains.

[0702] FIG. 23 shows the release profile of the tablets with the 7 mg weight gain of Final coating.

Study on Batch BUP-HBr-XL-174 mg-022-5

[0703] Using 174 mg tablets, an Ethocel coating followed by a final coating, were 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 30.

[0705] The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50° C.; Product Temperature: 35° C. $\pm$ 5° C.; and Supply Air Flow: 200 CFW.

[0706] It took 4 hours and 30 minutes to add a 30 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 29 mg, and 30 mg weight gains and were recorded in Table 31.

[0707] FIG. 24 shows the % dissolved of each of the samples with different weight gains of EC coating (22 mg, 24 mg, 28 mg and 30 mg weight gains). From the graph, it was evident that the tablets with the 30 mg weight gain of EC coating released slower than the other weight gains. When the release rates of the tablets with the 30 mg and the 28 mg weight gains were compared, there was only a slight difference noticed in the release. The f_2 similarity factor confirmed the similarity of the two releases (92.34%).

[0708] 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.

[0709] The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40° C.; Product Temperature: 35° C. $\pm$ 5° C.; and Supply Air Flow: 200 CFW.

[0710] It took 1 hour and 26 minutes to add a 7 mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded in Table 33 at 4 mg, 5 mg, 6 mg, and 7 mg weight gains.

[0711] The dissolution profile (FIG. 25) shows that the tablets with the 7 mg weight gain of final coating released the slowest, in comparison to the 5 mg and the 6 mg weight gains.

Study on Batch BUP-HBr-XL-348 mg-023-5

[0712] Using 348 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0713] 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.

[0714] The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50° C.; Product Temperature: 35° C. $\pm$ 5° C.; and Supply Air Flow: 200 CFW.

[0715] It took 2 hours and 16 minutes to add a 32 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 26 mg, 28 mg, 30 mg, and 32 mg weight gains and were recorded in Table 35.

[0716] The dissolution profile (FIG. 26) shows that the tablets with the 32 mg weight gain of EC coating, when compared to the tablets with the 26 mg, 28 mg and the 30 mg weight gain of EC coating, released at the slowest rate.

Study on Batch BUP-HBr-XL-348 mg-025-5

[0717] Using 348 mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0718] 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.

[0719] The parameters are as follows: Spray Rate: 13 g/min; Pan Speed: 12.0 rpm; Inlet Air: 50° C.; Product Temperature: 35° C. $\pm$ 5° C.; and Supply Air Flow: 200 CFW.

[0720] It took 2 hours and 13 minutes to add a 32 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 26 mg, 28 mg, 30 mg, and 32 mg weight gains and were recorded in Table 37.

[0721] The dissolution profile (FIG. 27) shows that the tablets with the 32 mg weight gain of EC coating when compared to those with 26 mg weight gain released slower in the beginning and then faster after 7 hours. When comparing the tablets with 32 mg weight gain of EC coating to those with 30 mg weight gain of EC coating, the tablets with the 32 mg weight gain released slower up until 10 hours. The f_2 similarity factor showed that the release of the tablets with the 30 mg and 32 mg weight gains were in fact similar (93.72%).

[0722] 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.

[0723] The parameters are as follows: Spray Rate: 6 g/min; Pan Speed: 12.0 rpm; Inlet Air: 40° C.; Product Temperature: 35° C. $\pm$ 5° C.; and Supply Air Flow: 200 CFW.

[0724] 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.

[0725] It took 40 minutes to add a 7 mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded (Table 39) at 4 mg, 5 mg, 6 mg, and 7 mg weight gains.

[0726] The dissolution profile (FIG. 28) shows that the tablets with the 7 mg weight gains released the slowest of the three samples tested. However, f_2 calculation showed that the tablets with the 6 mg weight gain released similarly to those with the 7 mg weight gain of Final coating (93.33%).

Study on Batch BUP-HBr-XL-348 mg-026-5

[0727] Using 348 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0728] 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.

[0729] 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.

[0730] It took 2 hours and 11 minutes to add a 32 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 26 mg, 28 mg, 30 mg, and 32 mg weight gains and were recorded in Table 41.

[0731] The dissolution profile (FIG. 29) shows that the tablets with the 32 mg weight gain of EC coating released the slowest when compared to the other three samples with lower weight gains of EC coating (26 mg, 28 mg and 30 mg).

[0732] Study on Batch BUP-HBr-XL-174 mg-027-5

[0733] Using 174 mg tablets, an Ethocel coating followed by a final coating, were sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0734] 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.

[0735] 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.

[0736] It took 3 hours and 29 minutes to add a 32 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 22 mg, 24 mg, and 26 mg weight gains and were recorded in Table 43.

[0737] The dissolution profile (FIG. 30) shows that the tablets with the 26 mg weight gain of EC coating released the slowest of the three samples tested.

[0738] 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.

[0739] 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.

[0740] It took 1 hour and 17 minutes to add a 7 mg weight gain of the final coating solution to the tablets. Tablet weights were taken and recorded in Table 45 at 4 mg, 5 mg, 6 mg, and 7 mg weight gains.

[0741] The dissolution profile (FIG. 31) shows that the tablets with the 7 mg weight gain of final coating initially released slower than the tablets with 4 mg, 5 mg and 6 mg weight gains. However, at approximately 12 hours, all 4 samples were releasing similarly.

Example 6

Bupropion HBr Enhanced Absorption (EA) Tablets

[0742] This example describes the development of bupropion EA "Enhanced Absorption" tablets (150 mg and 300 mg). Granulation, tableting 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.

[0743] 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.

[0744] The overall process for the development of bupropion HBr EA tablets is shown in FIG. 32.

Bupropion HBr EA—Granulation Process

[0745] A summary of the granulation process of the bupropion HBr EA tablets is shown in FIG. 33.

[0746] 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.

[0747] 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.

[0748] The Polyvinyl Alcohol was dissolved into the purified water using a magnetic stirrer and a clear colourless solution was made.

[0749] The NIRO Fluid Bed was used to granulate the Bupropion HBr Granules with the PVA solution in a process known as wet massing.

[0750] 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.

[0751] Loss on Drying was determined after each granulation using the Moisture Analyzer. A 1 g sample was taken

and loaded into the moisture analyzer. The sample ran for 5 minutes at a temperature of 105° C.

[0752] Upon completion of each batch part's granulation, the five parts were combined together. They were hand screened using Mesh No. 14 (1.4 mm) and any oversized granulation was passed through the Comil fitted with a 2 mm screen.

[0753] 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

[0754] The Beta Press was used to compress the Bupropion HBr tablets. Depending on the dose of the tablet, 150 mg or 300 mg, different tooling sets were used. The 7 mm punches were used to compress the 150 mg tablets and 9 mm punches were used to compress the 300 mg tablets. Tooling was polished prior to each run.

[0755] The tablet weights were determined as being 160.0 mg for the 150 mg dose tablets and 320.0 mg for the 300 mg 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 150 mg and 300 mg bupropion HCl tablets. The individual tablet weights had a control limit of $\pm 5\%$, and the average tablet weight had a control limit of $+3\%$ (using ten tablets).

[0756] 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 174 mg and 348 mg tablets.

[0757] Friability was determined using tablets that equaled a weight of 6.5 g 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.

[0758] 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.

[0759] Table 50 summarizes the specifications that were kept constant throughout the compression of all the batches.

Bupropion HBr EA—Coating Process

[0760] A summary of the coating process of the 150 mg and 300 mg bupropion HBr EA tablets with an Ethocel Coating is shown in FIG. 35.

[0761] 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.

[0762] 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.

[0763] 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).

[0764] 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).

[0765] 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).

[0766] 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).

[0767] Table 52 summarizes the specifications that were monitored in the coating process and their ranges.

In-Vitro Studies on the Bupropion HBr Cores

[0768] 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 900 mL of 0.1N HCl and at a speed of 75 rpm. 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.

[0769] 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 900 mL of Simulated Gastric Fluid (SGF) at pH 1.2 with 0.5% of Sodium Lauryl Sulfate (SLS), followed by 2 hours in 900 mL of Acetate Buffer at a pH of 4.5, followed by 12 hours in 900 mL 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

[0770] The formulation was granulated using NIRO Fluid Bed. The final blend was compressed into 300 mg tablets using the Beta press with 9 mm round, concave tooling and into 150 mg tablets with 7 mm round, concave tooling. Table 53 describes the amounts of each material in the granulation of the 300 mg tablets and Table 54 describes the amounts for the 150 mg 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 (FIG. 36). Dissolution was conducted on the 300 mg and 150

mg cores in order to determine their release (FIGS. 37 and 38, respectively). After granulation was completed, the batch was screened and then prior to compression, the lubricant (Compritol 888) was added.

[0771] 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 9 mm and 7 mm tooling respectively.

[0772] FIG. 36 shows that the different hardness ranges did not drastically affect the dissolution profiles. The dissolution profiles of the 300 mg (FIG. 37) and 150 mg cores (FIG. 38) show that the cores were releasing approximately 100 percent of API in an hour.

Study on Batch BUP-HBr-EA-300 mg-001-5

[0773] Using 300 mg Bupropion HBr core 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 57.

[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 4 minutes to coat the tablets with a weight gain of 54 mg. Tablet weights were taken and recorded in Table 58 at 44 mg, 46 mg, 48 mg, 50 mg 52 mg, and 54 mg weight gains.

[0777] The dissolution profile (FIG. 39) shows that the tablets with the 44 mg weight gain released the fastest and the tablets with the 54 mg weight gain released the slowest from the 6 different weight gains that were tested.

[0778] Dissolution using USP3 was also conducted on this trial, using the tablet with the 52 mg 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 (FIG. 40) showed that the trial did not match the in vivo data, nor did it match the Bupropion HCl data.

Study on Batch BUP-HBr-EA-150 mg-002-5

[0779] Using 150 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0780] 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.

[0781] 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.

[0782] The coating process of this trial took 4 hours and 38 minutes to obtain a 36 mg weight gain. Tablet weights were taken and recorded in Table 60 at 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg and 36 mg weight gains.

[0783] The dissolution profile (FIG. 41) shows that the tablets with the 18 mg and 20 mg weight gains of EC coating released the fastest of all the weight gains tested. It was the tablets with the 36 mg weight gain that released the slowest when compared to all the other weight gains.

Study on Batch BUP-HBr-EA-300 mg-003-5

[0784] Using 300 mg 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 61.

[0786] 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.

[0787] It took 4 hours and 13 minutes to add a 54 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 44 mg, 46 mg, 48 mg, 50 mg, 52 mg, and 54 mg weight gains and were recorded in Table 62.

[0788] The dissolution profile (FIG. 42) shows that the tablets with the 52 mg weight gain of EC coating released the slowest when compared to the other profiles with different weight gains.

Study on Batch BUP-HBr-EA-300 mg-004-5

[0789] Using 300 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0790] 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.

[0791] 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.

[0792] It took 4 hours and 13 minutes to add a 54 mg weight gain of the EC coating solution to the tablets. Tablet weights were taken at 44 mg, 46 mg, 48 mg, 50 mg, 52 mg, and 54 mg weight gains and were recorded in Table 64.

[0793] The dissolution profile (FIG. 43) shows that the tablets with the 52 mg weight gain released the slowest when compared to the other profile and the tablets with the 44 mg weight gain of EC coating released the fastest.

Study on Batch BUP-HBr-EA-300 mg-005-5

[0794] Using 300 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0795] 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.

[0796] 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.

[0797] It took 4 hours and 14 minutes to add a 54 mg weight gain of the EC coating solution to the tablets. Tablet

weights were taken at 44 mg, 46 mg, 48 mg, 50 mg, 52 mg, and 54 mg weight gains and were recorded in Table 66.

[0798] FIG. 44 shows that the tablets with the 54 mg weight gain released the slowest when compared to the other profiles and that the tablets with the 44 mg weight gain of EC coating released the fastest of the six profiles.

Study on Batch BUP-HBr-EA-150 mg-006-5

[0799] Using 150 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0800] 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.

[0801] 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.

[0802] The coating process of this trial took 4 hours and 36 minutes to obtain a 36 mg weight gain. Tablet weights were taken and recorded in Table 68 at 18 mg, 20 mg, 22 mg, 24 mg, 26 mg, 28 mg, 30 mg, 32 mg, 34 mg and 36 mg weight gains.

[0803] The dissolution profile (FIG. 45) shows that the tablets with the 36 mg weight gain of EC coating released the slowest when compared to the other four profiles (24 mg, 28 mg, 32 mg and 34 mg weight gains).

[0804] 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 300 mg target. The dissolution profile (FIG. 46) shows that the 150 mg Bupropion HBr EA tablets with 24 mg weight gain was close to the in vivo profile.

Study on Batch BUP-HBr-EA-150 mg-007-5

[0805] Using 150 mg tablets, an Ethocel coating was sprayed onto the tablets using the O'Hara Labcoat II Coating Equipment.

[0806] 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

[0807] 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.

[0808] Table 70 and FIG. 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 FIG. 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

[0809] Further forced degradation studies were carried out at 55° C., at 55° C. and 100% relative humidity, at 100° C., and at 105° C. 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 FIGS. 49-53. FIG. 49 shows the amount of 3-CBA impurity in the various samples. FIG. 50 shows the amount of 852U77 impurity in the various samples. FIG. 51 shows the amount of 20U78 impurity in the various samples. FIG. 52 shows the amount of 827U76 impurity in the various samples. FIG. 53 is a graph showing the loss of each salt over time in a TGA experiment at 100° C. 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.

[0810] 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

[0811] 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

[0812] The stability of bupropion HBr was evaluated under the accelerated conditions of 40° C.±2° C. 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'chloro-

ropropiophenone, 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

[0813] 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 25° C. +2° C. 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

[0814] 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:

[0815] 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 13 g 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 40° C. 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 (80° C.), to get complete solution of the suspended solid. The temperature was then lowered to 25° C. in 1 hour and further lowered to 0-5° C. 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 (30 mmHg) in a static drier at 50° C. for 16 hours. 34 g of bupropion hydrobromide form I were obtained.

[0816] 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 FIG. 60.

Form II:

[0817] 10 g of bupropion HBr form I were dissolved in a mixture of 170 ml 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 40° C. 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° C./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° C./75% r.h.). The crystalline form was checked after maintaining the product under these conditions for 1 month. The PXRD profile shown in FIG. 61 shows that the compound is still in form II. This demonstrates the stability of crystal form II under these conditions.

Form III:

[0818] 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 (30 mmHg) at 50° C. 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° C./75% r.h.). The crystalline form was checked after maintaining the product in these conditions for 1 month. The PXRD profile shown in FIG. 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

[0819] Formulation to be based on options used during the development of the Wellbutrin HCl SR 100 and 150 mg.

[0820] Bupropion HCl was replaced with HBr and adjusted to obtain same amount Bupropion base.

[0821] Filler materials adjusted accordingly in order to obtain the same tablet core weights.

e.g. 150 mg HCl=130 mg base=174 mg HBr

[0822] 100 mg=86.7=116

HBr Granulation Process:

[0823] 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.

[0824] The dry granules are then mixed with water soluble polymer or mixtures of hydrophobic/hydrophilic polymers at various viscosity grades. In trials used Hypromellose (Hydroxypropyl methylcellulose K4M CR grade) as well as Hydroxypropyl Cellulose (HPC) at quantities to obtain target release.

[0825] 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.

[0826] The compressed tablets are then coated with a non-functional colored film coating solution.

[0827] 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**

[0828] Stability of Bupropion HBr 348 Mg Tablets

[0829] 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.

[0830] 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:

[0831] 7 Counts: the 2M and 3M were similar to the initial and 6M similar to the 1M.

[0832] 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.

[0833] 90 Counts: Essentially lower dissolution profiles were observed for 2M, 3M, and 6M in comparison with the initial profiles. These results are contained in FIG. 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)

[0834] 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 dissolution 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 FIG. 64.

Example 16

Additional Open Dish-Closed Bottle Stability Studies

[0835] 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 FIG. 65.

Example 17

Dissolution of Bupropion Formulations According to the Invention in Different USP-3 Media

[0836] 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 FIG. 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 EC1 Lot # Bup-HBr-XL-012-5 (EC 32 mg wg) and Wellbutrin XL 300 mg tablets (EC10-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 FIG. 66-68.

[0837] Additionally, FIG. 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.

[0838] 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.

[0839] Also, FIG. 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 phosphate 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 3-continued

Solubility & other physical properties: Bupropion HBr vs Bupropion HCl.

Sample ID	PS (Malvern)	Moisture Content (KF)	pH (aq. 0.5%)	MP (DSC)
Bupropion HCl (Erregierre)	10%	32 μ m	0.01%	5.90
	50%	102 μ m		
	90%	276 μ m		
Bupropion HBr (Chemi)	10%	72 μ m	0.00%	5.92
	50%	245 μ m		
	90%	657 μ m		

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%

[0840]

TABLE 2

moisture content and pH of aqueous solutions:

Sample ID	Original (Initial APIs)		After re crystallization (R&D)		
	pH		Tested after 1 day		Tested after 2 Months
	KF	(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	0.23	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

[0841]

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

[0842]

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
--------------------------------	--	---	--

¹300 mg of the drug substance was placed in a 2 mL vial, then 100 mg placebo (almost double of the required amount) was added, and mixed well.

²Two drops of water was added to the spiked placebo and mixed well with a spatula, then closed with a cap.

³A 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 cap.

⁴A 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 cap.

[0843]

TABLE 5

API ID	Lot#	Quantity/bottle	# of glass bottle 40° C./ 75% RH	Stability pulling time (Day)
Bupropion HBr	STN07492	348 mg	2	14 & 24
Bupropion HCl	STN06973	300 mg	2	14 & 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

TABLE 105(6)-continued

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
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.

1-83. (canceled)

84. A stable bupropion pharmaceutical composition suitable for oral administration to a subject in need of bupropion therapy for treatment of a condition or palliating a disorder, comprising:

an effective amount of bupropion hydrobromide for treatment of the condition or palliating the disorder,

wherein the bupropion hydrobromide salt contained in said pharmaceutical composition is more stable than an otherwise identical pharmaceutical composition comprising the equivalent molar amount of a bupropion hydrochloride salt when each are stored for at least about 3 months at about 40 degrees C. and at about 75% relative humidity.

85. The stable bupropion pharmaceutical composition of claim 84 wherein said bupropion hydrobromide salt is more stable than an otherwise identical pharmaceutical composition containing bupropion hydrochloride when each are stored for at least about 6 months at about 40 degrees C. and at about 75% relative humidity.

86. The stable bupropion pharmaceutical composition of claim 84 which contains less of at least one degradation product characteristic of bupropion degradation after being stored at about 40 degrees C. at about 75% relative humidity than an otherwise identical pharmaceutical composition containing bupropion hydrochloride when stored under the same conditions.

87. The stable bupropion pharmaceutical composition of claim 84 which exhibits less fluctuations in the in vitro dissolution profile in at least one dissolution media than an otherwise identical pharmaceutical composition containing bupropion hydrochloride after each are stored for at least about 3 months at about 40 degrees C. and at about 75% relative humidity.

88. The stable bupropion pharmaceutical composition of claim 84 which is in the form of a tablet.

89. The stable bupropion pharmaceutical composition of claim 88, wherein the tablet is a modified release tablet.

90. The stable bupropion pharmaceutical composition of claim 89, wherein the modified release tablet is suitable for once daily oral administration.

91. The stable bupropion pharmaceutical composition of any one of claims 84-90 which comprises about 174 or about 348 mg of bupropion hydrobromide.

92. The stable bupropion pharmaceutical composition of claim 90, wherein said stable bupropion pharmaceutical composition comprises from about 50 mg to about 500 mg of bupropion HBr.

93. The stable bupropion pharmaceutical composition of claim 84, wherein the condition or disorder is selected from a group consisting of depression, smoking cessation, obesity and seasonal affective disorder.

94. A method of treating a subject in need of bupropion therapy, said method comprises

orally administering a stable bupropion pharmaceutical composition comprising an effective amount of bupropion hydrobromide to the subject in need thereof,

wherein the bupropion hydrobromide salt in said pharmaceutical composition is more stable when stored for at least about 3 months at about 40 degrees C. and at about 75% relative humidity than an otherwise identical pharmaceutical composition containing an equivalent molar amount of bupropion hydrochloride.

95. The method of claim 94, wherein said method is used to treat a condition selected from a group consisting of depression, smoking cessation, obesity and seasonal affective disorder.

96. The method of claim 94, wherein the pharmaceutical composition is more stable than an otherwise identical pharmaceutical composition containing bupropion hydrochloride when each is stored for at least about 6 months at about 40 degrees C. and at about 75% relative humidity.

97. The method of claim 94, wherein said pharmaceutical composition contains less of at least one degradation product characteristic of bupropion degradation after being stored

828

for at least about 3 months at about 40 degrees C. and at about 75% relative humidity than an otherwise identical pharmaceutical composition containing the same molar amount of bupropion hydrochloride.

98. The method of claim 94, wherein the pharmaceutical composition exhibits less fluctuations in the in vitro dissolution profile than an otherwise identical pharmaceutical composition containing the equivalent molar amount of bupropion hydrochloride after each are stored for at least about 3 months at about 40 degrees C. and at about 75% relative humidity.

99. The method of claim 94, wherein the pharmaceutical composition is in an oral dosage form.

100. The method of claim 99, wherein the oral dosage form is selected from the group consisting of a tablet or capsule.

101. The method of claim 100, wherein the pharmaceutical composition comprises about 174 or about 348 mg of bupropion hydrobromide.

102. The method of claim 94, wherein the pharmaceutical composition comprises from about 50 to about 500 mg of bupropion hydrobromide.

103. The method of any one of claims 99-102, wherein the stable bupropion pharmaceutical composition is a modified release composition.

104. The method of claim 103, wherein said administration step comprises administering the stable bupropion pharmaceutical composition to the subject once daily.

* * * * *

35