

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-009937-00000-0000

Fecha: 2011-01-28 16:41:52

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 411 PRESENTACION

Folios: 50

Industria y Comercio

SUPERINTENDENCIA

11-9937

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SOLICITUD DE PATENTE DE
INVENCION

TITULO: METODO NOVEDOSO

SOLICITANTE: GLAXOSMITHKLINE LLC

DIRECCIÓN: One Franklin, Plaza, 200 North 16th Street Philadelphia,
Pennsylvania 19102, Estados Unidos

APODERADO: CARLOS R. OLARTE

BOGOTÁ 28 de Enero de 2011

P2011/000025



No. 11-009937-00000-0000

Fecha: 2011-01-28 16:41:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 50

PETITORIO - FORMULARIO
PATENTE PCT
ENTRADA EN FASE NACIONAL
SOLICITUD DE:

P2011/000025

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)

Nombre: GLAXOSMITHKLINE LLC

Dirección: One Franklin Plaza, 200 North 16th
Street Philadelphia, Pennsylvania 19102

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos de
América.

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ **NIT** ☐

C.E. ☐ **Otro** ☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Diagonal 34 No. 5-28, Bogotá

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. ☒ **NIT** ☐

C.E. ☐ **Otro** ☐

Cual _____

Número 79782747Bta
TP 74.295

INVENTOR (ES)
(72)

Nombre: 1. GEOFFREY DUKE EDWARD CLARKE, 2. TIMOTHY JAMES
GRATTAN, 3. IAN BURNETT

Dirección: 1) 1500 Littleton Road, Parsippany, NJ 07054, E.U.A.

2 Y 3) C/o GlaxoSmithKline, St. George's Avenue, Weybridge, Surrey, KT13 0DE
Alemania

Nacionalidad o Domicilio: Británica

5

PCT (86)

Solicitud Internacional No. PCT/US2009/052039 Fecha Julio 29, 2009

Publicación Internacional No. WO 2010/014661 Fecha Febrero 4, 2010

6

Título (54) MÉTODO NOVEDOSO

Ver folio 54

Clasificación Internacional (51) A01N 37/18, A61K 31/16

Prioridad

SI

☒

NO

☐

(33) País de Origen

GB

(32) Fecha

Julio 30, 2008

(31) Número de Solicitud

08/139,297

9

Comprobante de pago No. 11-0007882

Fecha Enero 27, 2011



ANEXOS

9



Comprobante de pago de la tasa de presentación de la solicitud.



Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.



Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 10-057.587



Documento de cesión del inventor al solicitante o a su causante.



Declaraciones.



Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).



Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).



Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).



Traducción del examen preliminar internacional efectuado por la IPEA.



De ser el caso, copia del contrato de acceso.



De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.



De ser el caso, certificado de depósito del material biológico.



Arte final 12 x 12.



De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.



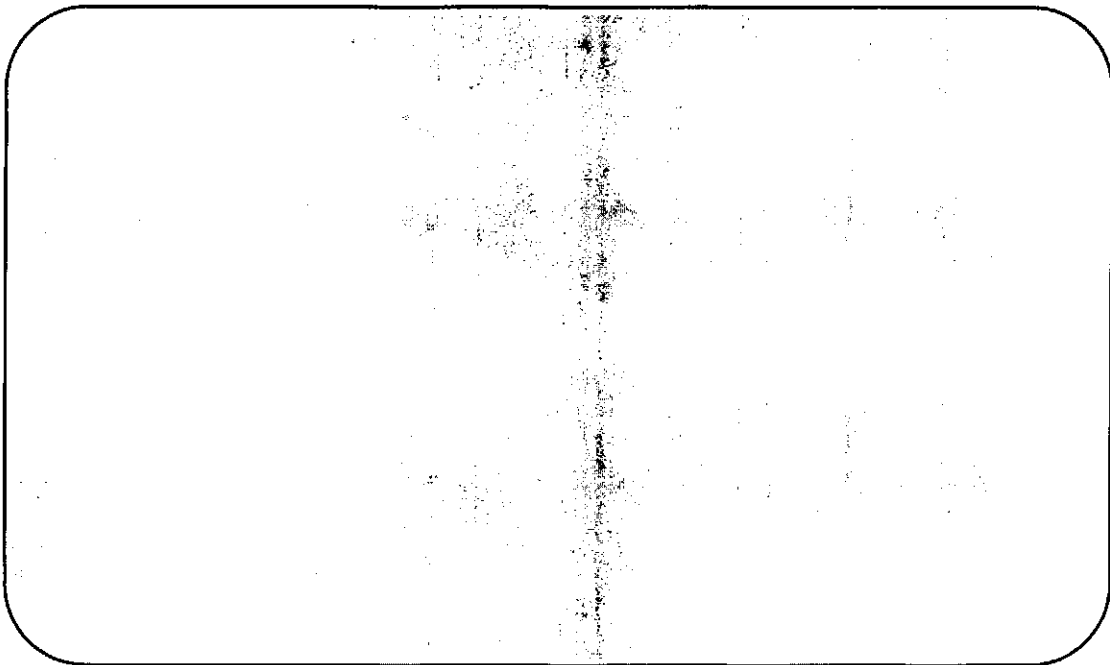
De ser el caso, modificaciones efectuadas a la solicitud internacional.



Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

3


Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 007882

Bogotá D.C., Enero 27 de 2011 - 16:16:22

RECIBIDO DE : OLARTERAISBECK

NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	353914455	27/01/2011	2.855.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	571.000.00	571.000.00
				\$571.000.00

SON: **QUINIENTOS SETENTA Y UN MIL PESOS MONEDA CORRIENTE***

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-009937- -00000-0000

Fecha: 2011-01-28 16:41:52 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACIÓN Folios: 50

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-810165 Call Center: (571) 6513240

, Enero 27 de 2011 - 16:16:22

Official translation of a document originally in Spanish
Apostilla adjunta:

APOSTILLA:	
(Convention de La Haye du 5 octobre 1961)	
1. País:	Estados Unidos de América
<u>El presente documento público</u>	
2. Ha sido firmado por:	Deborah A. Becker
3. Actuando en calidad de:	Notario Público
4. Lleva el sello/estampilla de:	Deborah A. Becker, Notario Público del Condado de Montgomery, Mancomunidad de Pensilvania.
<u>Certificado</u>	
5. En:	Harrisburg, Pensilvania.
6. El:	Día 9 de febrero de 2010
7. Por:	Pedro A. Cortés, Secretario de la Mancomunidad de Pensilvania.
8. Bajo el No.:	201003472
9. Sello / estampilla:	Gran sello del Secretario de la Mancomunidad de Pensilvania.
10. Firma:	Por: (Firmado) Pedro A. Cortés

FIN DE LA TRADUCCIÓN

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual
he elaborado según mi leal saber y entender.
Documento: "Apostilla"
Fecha: 25 de febrero de 2010.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de
Relaciones Exteriores de Colombia)
Licencia # 376 de 1998, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-18 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2908, (571) 628 2925.
E-mail: trascor116@yahoo.com
Traducción # 14-618

Traductor
JORGE E. SIERRA R.
Licencia 376-1998 Ali

5

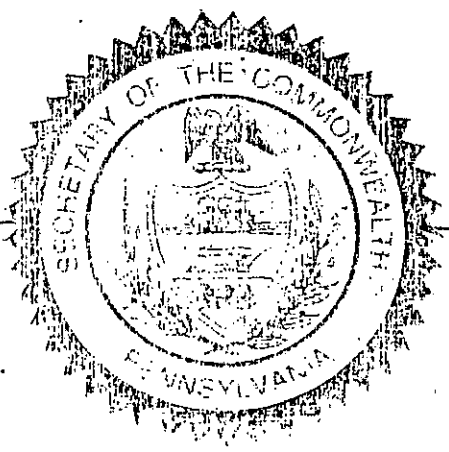
APOSTILLE
(Convention de La Haye du 5 octobre 1961)

- 1. Country : United States of America
- 2. This public document has been signed by DEBORAH A BECKER
- 3. acting in the capacity of NOTARY PUBLIC
- 4. bears the seal/stamp DEBORAH A BECKER , NOTARY PUBLIC, MONTGOMERY COUNTY, COMMONWEALTH OF PENNSYLVANIA
- 5. at Harrisburg, Pennsylvania
- 6. The 9th day of February, 2010
- 7. by Pedro A. Cortés, Secretary of the Commonwealth of Pennsylvania
- 8. No: 201003472
- 9. Seal/Stamp
- 10. Signature

Certified

Pedro A. Cortés

Pedro A. Cortés



6
Carlos R. Olarte
J. Ian Raisbeck
Juan Guillermo Moure
Natalia Castro

Power of Attorney

The undersigned,

domiciled in

One Franklin Plaza, 200 North 16th Street Philadelphia, Pennsylvania 19102
by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

El suscrito,
GLAXOSMITHKLINE LLC

domiciliado en

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** poder amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Edward R. Gimmi

Date/Fecha: 18 January 2010

City/Country/Ciudad, País: King of Prussia, Pennsylvania, USA

Alexander Agudelo
Catalina Barbastefano
Ángela Correa
Erika Rico
Carlos A. Parra
Andrés Alvarado
Gina Arias
Juan Felipe Acosta
Andrés Rincón
Grace García
Mariana Franco
Of Counsel
Guillermo Chahín
Graciela Melo
Jacqueline Chaparro

X

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

Certificación Notarial

On this date,
18 January 2010

En esta fecha,

The undersigned Notary Public certifies:

el Notario Público suscrito certifica:

1. That

1. Que

Edward R. Gimmi

of legal age and domiciled in

mayor de edad y domiciliado

709 Swedeland Road, King of Prussia, Pennsylvania, USA

signed the foregoing document.

suscribió el documento que antecede.

2. That the grantor has executed the foregoing document as Authorized Attorney and Signatory of GlaxoSmithKline LLC

2. Que el otorgante ha suscrito el referido documento en su carácter de

de

3. That GlaxoSmithKline LLC, having its principal place of business located in Philadelphia, Pennsylvania, USA is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

3. Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature) Deborah A. Becker

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Deborah A. Becker, Notary Public
Upper Merion Twp., Montgomery County
My Commission Expires April 6, 2012
Member, Pennsylvania Association of Notaries

8

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 February 2010 (04.02.2010)

PCT

(10) International Publication Number
WO 2010/014661 A1

(51) International Patent Classification:
A01N 37/18 (2006.01) A61K 31/16 (2006.01)

(21) International Application Number:
PCT/US2009/052039

(22) International Filing Date:
29 July 2009 (29.07.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08/139,297 30 July 2008 (30.07.2008) GB

(71) Applicant (for all designated States except US):
SMITHKLINE BEECHAM CORPORATION
[US/US]; One Franklin Plaza, P.o. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): CLARKE, Geoffrey Duke, Edward [GB/US]; 1500 Littleton Road, Parsippany, NJ 07054 (US). GRATIAN, Timothy, James [GB/GB]; C/o Glaxosmithkline, St. George's Avenue, Weybridge, Surrey, KT13 0DE (GB). BURNETT, Ian [GB/GB]; C/o Glaxosmithkline, St. George's Avenue, Weybridge, Surrey, KT13 0DE (GB).

(74) Agents: DINNER, Dara, L. et al.; c/o Glaxosmithkline, Corporate Intellectual Property, UW2220, 709 Swedeland

Road, P.o. Box 1539, King Of Prussia, PA 19406-0939 (US).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: NOVEL METHOD

(57) Abstract: The present invention is directed to a novel method for reducing inpatient variability in pharmaceutically active agent which is suitably not absorbed in the stomach, such as paracetamol, containing formulations in patients having gastric dysmotility, or a method of improving analgesia in a diabetic patient, or improving absorption of an active agent in a patient with gastric dysmotility, which methods comprises administering orally to said patient in need thereof a pharmaceutical dosage form comprising a first active agent, calcium carbonate, at least one first binding agent, and at least one disintegrating agent as intragranular components in the form of a granulate, and as an extragranular component at least one hydrophilic colloid, an optionally a second binding agent, calcium carbonate, a super disintegrant, and a second active agent.



WO 2010/014661 A1

NOVEL METHOD

FIELD OF THE INVENTION

The present invention is directed to novel methods of use for paracetamol containing
5 formulations which deliver rapid dissolution of the active agent followed by improved
absorption in patients with delayed gastric emptying.

BACKGROUND OF THE INVENTION

The present invention is the use of a paracetamol formulation that has unexpectedly been
10 shown to have improved pharmacokinetic profiles in patients having gastric dysmotility
or gastroparesis. Historically, diabetes has been shown to reduce gastric motility
(gastroparesis) by up to 50% in patients as compared to non-diabetic individuals.

Involvement of the autonomic nervous system in patient having diabetes mellitus includes
15 gastric enteropathy characterized by gastrointestinal dysmotility. Bassotti, G., Recenti
Prog Med. 82: 334-337 (1991). Long-standing diabetes mellitus may reduce gastric
emptying in up to 50% of patients. O'Mahony et al., Drugs Aging, 19: 515-527 (2002).
The impact of various age-related diseases on gastrointestinal motility in the elderly can
also include those patients with depression which significantly prolongs whole-gut transit
20 time; hypothyroidism, chronic renal failure, and idiopathic Parkinson's disease.
Frequently drugs in the elderly can cause disordered gastrointestinal motility, such as
anticholinergics, opioid analgesics and calcium antagonists.

The importance of dysmotility in patients, particularly the elderly, may result in serious
25 clinical consequences where clinical response to a medication is delayed, such as in
delayed levodopa absorption or with diuretics. As opioids and anticholinergics already
have inhibitory effects on gastric emptying, this may delay the absorption of other drugs.
Consequently, the need for consistent, low inpatient variability on absorption of drugs,
such as analgesics, in such a patient population is very much in need.

30

SUMMARY OF THE INVENTION

The present invention is directed to a novel method for reducing inpatient variability in
pharmaceutically active agent which is suitably not absorbed in the stomach, such as
paracetamol containing formulations in patients having gastric dysmotility, and the
35 present invention is directed to a method for improving analgesia in a diabetic patient, or
for improving absorption of an active agent in a patient with gastric dysmotility, which
methods all comprises administering orally to a patient in need thereof, a pharmaceutical
dosage form comprising a first active agent, suitably paracetamol, calcium carbonate, at

d

least one first binding agent, and at least one disintegrating agent as intragranular components in the form of a granulate, and as an extragranular component at least one hydrophilic colloid, an optionally a second binding agent, calcium carbonate, a super disintegrant, and a second active agent.

5

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a novel method of improving the variability of absorption of an active agent between patients who have gastric dysmotility. Gastric dysmotility is also known as gastric hypomotility. Gastric hypomotility, in otherwise normal patients, can be induced by a variety of environmental, pharmacological and physiological factors. Importantly, delayed gastric emptying can have a deleterious effect on the absorption of drugs such as paracetamol, which are absorbed primarily in the small intestine. This can result in delayed and inconsistent plasma levels of a medicine, and can cause discomfort when the particular medicine is a pain medicine such as paracetamol.

15

For purposes herein the active agent is suitably not one which is absorbed in the stomach. The present formulation is intended to introduce the active agent into the duodenum at an increased rate over an otherwise standard formulation of the active agent. Therefore, any active that is absorbed primarily after the pyloric sphincter (e.g., at the bottom of the stomach) rather than in the stomach itself is expected to show a more rapid, and a more consistent pharmacokinetic profile. As will be described herein in greater detail, the active agent, paracetamol has been chosen herein to describe the invention. Paracetamol in a standard dosage form has been shown to not contribute to the emptying rate of the drug from the stomach.

25

Paracetamol is an analgesic and antipyretic drug effective in relieving mild to moderate pain. The recommended therapeutic dose in the United Kingdom is 500-1000 milligrams (mg) every 4 to 6 hours (hr) up to a maximum of 4000mg daily. The absolute oral bioavailability is about 80% and is independent of dose in the range of 5-20mg/kg. Peak plasma levels are achieved between 0.5 and 3 hour post-dose depending on the formulation.

30

Paracetamol has a mean plasma half-life of 2.4 hours in adults with a range of 1.5-3.0 hours. It varies relatively little between individuals, and is not prolonged to a clinically significant extent at the extremes of age. It is not bound to plasma protein to any extent and the volume of distribution is about 0.9 litre/kilogram (l/kg) body weight.

35

Oral paracetamol is primarily absorbed from the upper small intestine and for standard solid dose tablet formulations the rate of absorption is limited by i) the process of tablet disintegration/dissolution and ii) by gastric emptying from the stomach into the upper small intestine.

5

Diabetes mellitus (type 2) is the most common cause of impaired gastrointestinal motility in the elderly. Gastric emptying can be abnormal in this population and therefore impact on the absorption profile of the active agent, such as paracetamol. The present invention has investigated the absorption profile of paracetamol from a standard dosage form and
10 from a granulate dosage form of paracetamol and calcium carbonate, and has determined that the relative difference in absorption profiles observed in healthy volunteers is changed when using diabetic patients as a model of gastric dysmotility.

15

One embodiment of the present invention is directed to the use of a granulate composition of paracetamol as will be further described herein, that has now been shown to provide significantly greater absorption at 30 minutes, and to have statistically significant Cmax plasma levels at 30 minutes over standard paracetamol containing formulations in patients have gastric dysmotility. In one embodiment of the invention, those patients having gastric dysmotility are diabetic patients.

20

The present invention has also shown to provide significantly greater absorption at 60 minutes over standard paracetamol containing formulations in patient have gastric dysmotility.

25

While the present invention has also been shown to have a shorter time to maximal concentration (Tmax) as compared to standard paracetamol, however, the difference was not statistically significant. Overall the diabetic population shows slower absorption of paracetamol from both treatments when compared with results observed in healthy volunteers and this could be attributed in part to the gastric enteropathy that is known to
30 occur in diabetes mellitus. Therefore, patients with type 2 diabetes are a suitable dysmotility model which can be used to evaluate the PK profile of paracetamol from two different formulations.

35

The paracetamol containing dosage form comprises paracetamol, calcium carbonate, at least one binding agent, and at least one disintegrating agent, as intragranular components in the form of a granulate, and as an extragranular component, a hydrophilic colloid, an optionally a binding agent, calcium carbonate, a super disintegrant, and/or additional

9

paracetamol. A formula containing such excipients has been described in WO 2007/118063, filed 3rd April 2007 whose disclosure is incorporated by reference herein in its entirety.

5 While not wishing to be limited to such a dosage form, it is also believed that the paracetamol containing dosage forms as described in Roberts et al., US 2007/0141144, published June 21, 2007 or an earlier but related WO publication, WO 2005/15344, published 8 December 2005, whose disclosures are incorporated by reference herein, are also acceptable for use in the methods described herein.

10

A fast release composition according to this invention disintegrates and dissolves rapidly in the stomach so as to facilitate fast absorption of the active agent into the circulatory system. For purposes herein, "fast release" means wherein at least 60% of the active has dissolved from the composition at 180 seconds, as determined by the dissolution testing method described herein. In another embodiment, suitably at least 70%, of the active has dissolved. In another embodiment at least 80% has dissolved, and in yet another embodiment at least 90% of the active agent has dissolved from the composition at 180 seconds. A suitable dissolution testing method for this purpose utilizes the same conditions as disclosed in WO 02/100391, namely a USP paddle apparatus rotating at 30 rpm, employing 900ml of 0.05M HCl at 37° C as the dissolution medium. In this reference, the percentage of paracetamol dissolved was determined at fifteen minutes, rather than the 180 seconds as described in US 2007/0141144. Also noted as suitable are the dissolution methods described at 5, 10, 15, 20, 25 and 30 minutes in Rostami-Hodjegan et al., Drug Development and Industrial Pharmacy, 28(5), pp 533-5439 (2002).

25

While paracetamol release rates have been determined for a number of commercially available paracetamol products and found to range from about 12% to about 32%, a fast release of the active is only part of the present invention. Not only must the active be released from its dosage form, the active must also be emptied from the stomach into the duodenum at a rate which is consistent from patient to patient, and in particular in patients with decreased gastric motility be emptied as near normal as possible.

30

Accordingly one aspect of the invention provides for a pharmaceutical composition comprising an active, calcium carbonate, at least one binding agent, and at least one disintegrating agent, as intragranular components in the form of a granulate.

35

The granulate may optionally be combined with one or more suitable extragranular components, and may be in the form of a "tablet" which may include tablet of any shape, and includes caplets, which are tablets having a capsule shape. The formulation may be placed into capsules, or be available in unit dose sachets.

5

When in a unit dosage form, a composition according to the invention comprises a therapeutically effective amount of the active. In one embodiment the active is paracetamol, by which is meant an amount of paracetamol sufficient to achieve a therapeutic benefit. Suitably such an amount is in the range 250 mg to 1000mg per unit dosage form (e.g. per tablet) and typically is either 325 mg or 500 mg.

10

While the active is present as an intragranular component, it is recognized that a limited amount of the same or a different active, may also be present extragranularly. Although it has not been prepared and tested, another embodiment of the invention includes a formulation wherein the active agent is solely dispersed in the formulation as extragranular component.

15

A pharmaceutical composition according to the invention comprises intragranular calcium carbonate. Suitably the calcium carbonate content in the granulate does not exceed 20.0% by weight of the composition, and for example in one embodiment is present in an amount of about 5.0% to about 20.0% by weight, suitably from about 5.0% to about 15.0% by weight of the composition. In an alternative embodiment the calcium carbonate content is from about 8.0% to about 15.0% by weight of the composition.

20

In one embodiment according to the invention the paracetamol content in the granulate is in the range 70.0 to 80.0 % by weight of the composition and the calcium carbonate in the granulate is in the range 8.0% to 15.0% by weight of the composition. For example a 500mg paracetamol composition may comprise 30mg to 110mg intragranular calcium carbonate, and a 325mg paracetamol composition may comprise intragranular 20mg to 72mg calcium carbonate.

25

While calcium carbonate is present as an intragranular component, it is recognized that a limited amount of calcium carbonate e.g. up to about an additional 25.0% by weight of the intragranular calcium carbonate content of the composition, may also be present extragranularly. In one embodiment a composition according to the invention comprises, as an extragranular component, calcium carbonate in an amount ranging from about 0.1% to about 10.0% by weight of the intragranular calcium carbonate amount therein.

30

35

A composition according to the invention comprises intragranularly, a component that functions as a binder, such as one or more binding agents. Suitably the binding agent may comprise a first binding agent and a second binding agent. Suitable binding agents for use herein include conventional binding agents used in the art such as starches, polymers and cellulose derivatives or combinations thereof.

If the binding agent includes a starch, suitably it is of vegetable origin such as corn (or maize) starch, modified corn starch, wheat starch, modified wheat starch, potato starch, or pregelatinized starch e.g. available commercially as Starch 1500 G or Prejel; or a combination of two or more thereof.

Combinations of starch with other binding agents, such as those described herein, are also envisaged within the scope of the invention. In one embodiment, suitably the starch is pregelatinized starch, where it is the sole or a first binding agent. Pregelatinized starch is a starch that has been chemically and/or mechanically processed. Typically pregelatinized starch contains 5% of free amylase, 15% of free amylopectin, and 80% unmodified starch. Pregelatinized starch may be obtained from corn (or maize), potato or rice starch. It has been found that paracetamol dissolution rate is adversely affected in a composition comprising as intragranular components: paracetamol, calcium carbonate, maize starch, pregelatinized starch, Povidone K25, and potassium sorbate, wherein the weight ratio of pregelatinized starch to maize starch is about 2.3: 1. Accordingly if the binding agent comprises a mixture of corn (or maize) starch and pregelatinized starch, then the weight ratio of pregelatinized starch to corn (or maize) starch is at least 3.0:1.0. In one embodiment of this invention, the weight ratio of pregelatinized starch to corn (or maize) starch is at least 5.0:1.0.

Suitably, when present in a composition of the invention, the starch is present in the granulate in an amount from about 1.0% to about 30.0% by weight of the composition, typically from about 5.0% to about 20.0% for example from about 8.0% to about 15.0% by weight of the composition.

If the binding agent includes a polymer, suitably it is polyvinyl pyrrolidone or povidone (PVP), polyvinyl alcohol (PVA), polyethylene oxide, polaxamer, polymethacrylate e.g. a carbomer, polyethylene glycol (PEG) such as PEG 3350 and calcium polycarbophil; or a combination of two or more thereof. Combinations of a polymer with other binding agents, such as those described herein, are also envisaged within the scope of the

invention. When the polymer comprises PVP, it will suitably comprise a molecular weight of about 30,000 e.g. available commercially as PVP K25. Suitably, when present in a composition of the invention, the polymer is present in the granulate in an amount from about 1.0% to about 10.0% by weight of the composition, typically from about 1.5%
5 to about 5.0% by weight of the composition.

In one embodiment, a polymer such as PVP is present as a second binding agent. In one embodiment a starch such as pregelatinized starch is present as a first binding agent, in an amount ranging from about 10.0% to about 15.0% by weight of the composition, and a
10 polymer such as PVP is present as a second binding agent in an amount ranging from about 1.5% to about 5.0% by weight of the composition. Suitably such an embodiment is substantially free of corn (or maize) starch, for example comprising no more than an amount ranging from about 0.0% to about 1.0% of corn (or maize) starch.

15 If the binding agent includes a cellulosic derivative, suitably it includes at least one of hydroxypropyl cellulose (HPC) (low to medium viscosity versions thereof) e.g. as may be available commercially under the brand name Klucel® from the Aqualon division of Hercules Inc., Dow Chemical Company e.g. Klucel GF, Klucel JF, Klucel LF and Klucel EF; hydroxypropylmethyl cellulose (HPMC) (low to medium viscosity versions thereof)
20 e.g. as may be available commercially under the brand name Methocel® from the Dow Chemical Company e.g. Methocel E15Premium, Methocel E3Premium LV, Methocel K100LV; microcrystalline cellulose (MCC), carboxymethylcellulose (MC), sodium carboxymethylethyl cellulose; or a combination of two or more thereof. Combinations of a cellulosic derivative with other binding agents noted above are also envisaged within
25 the scope of the invention.

The term "low to medium" viscosity as used herein means a viscosity in the range of from about 15 to about 1000 mPa.s. It is recognized in the art that the determination of the viscosity of cellulosic derivatives is based upon standard techniques and grading in the art
30 e.g. for HPMC, viscosity may be determined at 20°C with a 2% solution using a Ubbelohde viscometer, or for HPC, viscosity may be determined at 25°C with a 2-10% solution using a Brookfield LVF viscometer. Generally the cellulosic derivative is present in the granulate in an amount ranging from about 0.5% to about 5.0% by weight of the composition. It is recognized in the art that certain cellulosic derivatives, such as
35 HPMC, will have varying roles in a formulation, depending upon the amount used. For example HPMC (low or medium viscosity) may function as a binding agent, a coating agent, or as a matrix forming agent. It has been found that when HPMC (low or medium

12

viscosity) is used at about 10.0% by weight of the composition, the dissolution rate of paracetamol is slowed down, probably owing to the extended-release properties of HPMC. According to the present invention, when used as a binding agent, the HPMC is present in an amount typically not more than 2.5% by weight of the composition, for example in an amount from about 1.0% to about 2.5% by weight of the composition.

The total amount of binding agent present intragranularly in a composition according to the invention is suitably in an amount ranging from about 1.0% to about 30.0% by weight of the composition, for example from about 2.0% to about 25.0 % by weight of the composition, or alternatively from about 5.0% to about 20.0% by weight of the composition.

While a binding agent is present as an intragranular component, it is recognized that a modest amount of binding agent e.g. up to about an additional 5.0%- 10.0% by weight of the intragranular binding agent content of the composition, may also be present extragranularly. In one embodiment a composition according to the invention comprises, as an extragranular component, a binding agent in an amount ranging from about 0.1% to about 10.0% by weight of the intragranular binding agent amount therein.

A composition according to the invention comprises, as an intragranular component, at least one component one that functions as a disintegrant, and may include at least two disintegrating agents. Suitable disintegrating agents include a non-super disintegrant, a super disintegrant or a combination of both. Suitable non-super disintegrants include conventional disintegrants such as starch (corn or maize), pregelatinized starch, e.g. Starch 1500 G, clays (Veegum or Bentonite), microcrystalline cellulose, cellulose or powdered cellulose. It is recognized in the art, that some excipients may perform more than one role in a given pharmaceutical formulation. For example certain excipients, e.g. starches including pregelatinized starch, and microcrystalline cellulose (hereinbefore identified as binding agents) function as both binders and disintegrants. Accordingly it will be understood that the same excipient may act as both a binding agent and a disintegrating agent. In such cases, inclusion of a disintegrating agent in addition to a binding agent is entirely optional. Equally, in such cases, inclusion of a binding agent in addition to a disintegrating agent is entirely optional.

One embodiment of the invention provides for as intragranular components, paracetamol and calcium carbonate, and at least one binding agent which is microcrystalline cellulose or starch, wherein the starch is corn (or maize) starch, modified corn starch, wheat starch,

modified wheat starch, potato starch, pregelatinized starch or a combination of two or more starches thereof, with the proviso that if the binding agent comprises a mixture of corn (or maize) starch and pregelatinized starch then the weight ratio of pregelatinized starch to corn (or maize) starch is greater than from about 3.0 to 1.0; and optionally a
5 disintegrating agent; and one or more pharmaceutically acceptable ingredients as extragranular components.

The compositions herein may include a non-super disintegrant which may be present intragranularly, extragranularly or both intragranularly and extragranularly. When a non-
10 super disintegrant is either absent from the composition or is present only extragranularly, the disintegrating agent will suitably comprise a super disintegrant, present intragranularly.

Suitably a non-super disintegrant will be present intragranularly in an amount ranging
15 from about 5.0% to about 30.0% by weight of the composition, suitably from about 5.0% to about 20.0% by weight of the composition. When present extragranularly, the non-super disintegrating agent, may also be present in an amount for example up to about an additional 5.0% - 10.0% by weight of the intragranular non-super disintegrating agent content of the composition.

20 A super disintegrant, if used, may be present intragranularly, extragranularly or both intragranularly and extragranularly. It is recognized that when a super disintegrant is either absent from the composition or is present only extragranularly, the disintegrating agent will comprise a non-super disintegrant, present intragranularly. A super
25 disintegrant may be used intragranularly or extragranularly, in an amount ranging from about 0.5% to about 5.0% by weight of the composition. The total amount of super disintegrant may be in an amount ranging from about 0.5% to about 10.0% by weight of the composition.

30 "Super disintegrants" represent a class of disintegrating agent which may generally be used in lower amounts in pharmaceutical preparations, as compared to conventional disintegrants. Examples of super disintegrants include sodium starch glycolate; the sodium salt of carboxymethyl starch, modified cellulose and cross-linked polyvinyl pyrrolidone. Sodium starch glycolate is available commercially under the trade names
35 Explotab® (Edward Mendell Co.), Primojel® (Generichem Corp) and Tablo® (Blanver, Brazil). An example of modified cellulose includes croscarmellose, the sodium salt of carboxymethyl cellulose. Croscarmellose is available commercially under the trade

B

names AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Netherlands), Primellose® (Avebe, Netherlands), Solutab® (Blanver, Brazil). An example of a cross-linked polyvinyl pyrrolidone includes crospovidone, and is commercially available under the trade names Kollidon CL® or Kollidon CL-M (BASF Corp.), and Polyplasdone XL® (ISP Corp). Suitably the disintegrating agent comprises cross-linked polyvinyl pyrrolidone.

A composition according to the invention may optionally contain further additional pharmaceutically acceptable extragranular components. For example a composition according to the invention may comprise a hydrophilic colloid such as alginic acid, carageenan, gellan, pectin and/or agar, as an extragranular component. Suitably the hydrophilic colloid is alginic acid. When present, a hydrophilic colloid is present in an amount ranging from about 1.0% to about 5.0% by weight of the composition.

In one aspect a composition according to the invention comprises alginic acid as an extragranular component.

Other pharmaceutically acceptable extragranular components include, but are not limited to, an antimicrobial agent e.g. potassium sorbate or a paraben i.e. one or more hydroxy benzoic acid esters e.g. methyl, ethyl, propyl or butyl, suitably singularly or as mixtures. In one embodiment of the invention a paraben is used.

In one embodiment the composition comprises paracetamol, calcium carbonate, pregelatinized starch, and povidone as intragranular components, and as extragranular components alginic acid and crospovidone, and optionally other extragranular components, preferably compressed into a tablet. Suitably, the alginic acid is present in an amount ranging from about 1.0% to about 5.0% by weight of the composition.

Additional pharmaceutically acceptable extragranular components include a dye; colorant; flavorant; compression aid; preservative; wetting agent; bulking agent; adhesive; sweetening agent; lubricant such as magnesium stearate, calcium stearate, sodium stearate, stearic acid or talc; and a flow aid or glidant such as colloidal silicon dioxide (Cab-O-Sil, Syloid™). Suitably, when present, a lubricant or flow aid are each used in an amount ranging from 0.1% to 5.0% by weight of the composition. It is recognized that additional pharmaceutically acceptable components may be present as intragranular components as well as extragranular components.

In addition to paracetamol, compositions of the invention may also contain other pharmaceutically active agents for example other analgesics such as codeine, hydrocodone, oxycodone, tramadol and propoxyphene; anti-inflammatory analgesics such as NSAIDs e.g. aspirin and ibuprofen; decongestants such as pseudoephedrine and
5 phenylephrine; antitussives such as pholcodine and dextromethorphan; expectorants such as guaifenesin and bromhexine; diuretics such as pamabrom; non-sedating and sedating antihistamines such as diphenhydramine, doxylamine and mepyramine; gastrointestinal agents such as metoclopramide; triptans such as sumatriptan; and muscle relaxants such as methocarbamol; and adjuvants, for example caffeine. As previously noted,
10 pharmaceutically active agents and adjuvants may be present intragranularly, extragranularly or both intragranularly and extragranularly.

In another aspect there is provided a composition comprising caffeine intragranularly, extragranularly or both intragranularly and extragranularly. Suitably the caffeine is
15 present extragranularly. In one embodiment the caffeine is in addition to an intragranular paracetamol containing formulation.

As used herein the term "pharmaceutically active agent" includes, but is not limited to, drugs, dietary supplements, vitamins, minerals, nutraceuticals, and veterinary agents.
20 This term includes bioactive agents, active agents, therapeutic agents, or drug(s) as defined herein, and follows the guidelines from the European Union Guide to Good Manufacturing Practice. Such substances are intended to furnish pharmacological activity or other direct effect in the cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. The pharmacological activity may be
25 prophylactic, or for treatment of a disease state.

Drug substances include those intended for oral administration. A description of these classes of drugs and a listing of species within each class can be found in Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, London, 1989.
30 The drug substances are commercially available and/or can be prepared by techniques known in the art.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the
35 present invention.

EXAMPLE 1

Pharmacokinetic Profile in Gastric Dysmotility Patients

Long standing diabetes may have reduced gastric motility by up to 50%. Therefore, patients with type 2 diabetes were chosen as a dysmotility model to evaluate the PK profile of paracetamol from two different formulations. This study was a single centre, two way, open label, randomized, single dose, cross over PK study. Subjects received a single 1 gm oral dose of a formulation of the invention or standard paracetamol formulation, 2 hours after a standard meal, with randomly assigned patients having a 24 hour wash out between dosing. 21 patients completed the protocol, 18 males, and 3 females. Blood samples were taken 4 hours post-dose for pharmacokinetic analyses.

The primary study objective was to compare early exposure, as assessed by rate of absorption (area under the curve [AUC]_{0-30 mins}). Other early exposure variables included time to maximum concentration (T_{max}), and inter-patient variability (coefficient of variation (CV)) in AUC_{0-30 mins}, AUC_{0-60 mins} and plasma concentration (C_{plasma}) at 30 minutes.

Standard Panadol tablets are film coated tablets containing 500mg paracetamol, and contain as excipients, pregelatinized starch, maize starch, talc, stearic acid, povidone, potassium sorbate, hypromellose, and glycerol triacetate.

The calcium carbonate/paracetamol formulation used herein contains 500mg paracetamol and is similar to that described in Example 6 of WO 2007/118063.

Results:

Parameter	Paracetamol/Calcium Carbonate Formula (n=21) mean, median, CV%	Panadol Standard (n=21) mean, median, CV%	Median difference	p-Value (Wilcoxon test)	p-Value (CV Square Rank test)
AUC0-30min (ug/ml.h)	0.45, 0.28, 153.1	0.14, 0.04, 215.8	0.18	0.0004	0.0522
AUC0-60min (ug/ml.h)	2.10, 1.38, 102.8	0.84, 0.26, 174.9	1.02	0.0014	0.0801
Cplasma at 30 mins (ug/ml)	2.48, 1.52, 125.0	0.84, 0.19, 282.7	1.08	0.0002	0.0693
Tmax (h)	2.36, 2.50, 41.4	2.77, 2.75, 33.5	-0.25	0.1448	-
Cmax (ug/ml)	8.99, 7.97, 34.9	9.49, 9.77, 28.9	-	-	-
AUC0-tmin (ug/ml.h)	21.01, 18.92, 35.1	18.5, 16.04, 7.9	-	-	-

AUC₀₋₃₀ min (primary objective) was statistically significantly greater for the Paracetamol/calcium carbonate containing formulation than for standard paracetamol (p=0.0004).

- 5 AUC₀₋₆₀ min and C_{plasma} at 30 minutes were statistically significantly greater (p=0.0014) and higher (p=0.0002), respectively, for Paracetamol/calcium carbonate containing formulation compared to standard paracetamol.

- 10 The time to maximum concentration (T_{max}) was shorter for Paracetamol/calcium carbonate containing formulation compared to standard paracetamol but the difference was not statistically significant (p=0.1448).

- 15 There was a trend towards statistical significance for the comparison of CVs for AUC₀₋₃₀ min (p=0.0522), AUC₀₋₆₀ min (p=0.0801) and C_{plasma} at 30 minutes (p=0.0693) in favour of Paracetamol/calcium carbonate containing formulation.

- 20 The Paracetamol/calcium carbonate containing formulation was absorbed more rapidly than standard paracetamol tablets, and demonstrated a trend towards less inter-patient variability (based on the coefficient of variation) in this population of diabetic patients.

- 25 The planned sample size was less than desired, and may explain why there was a lack of statistical significance for the T_{max} comparison obtained. Overall the tested population (diabetics) in this study showed slower absorption of paracetamol from both treatments when compared with results observed in healthy volunteers and this could be attributed in part to the gastric enteropathy that is known to occur in diabetes mellitus. However, the paracetamol/calcium carbonate containing formulation appears to maintain the advantages of fast and consistent absorption shown in previously healthy volunteers, even in those patients with diabetes mellitus.

30 **EXAMPLE 2**
Pharmacokinetic Parameter Study

- 35 It had previously been determined in a clinical study that the Paracetamol/calcium carbonate containing formulation (as described above) is emptied from the stomach more rapidly than a standard paracetamol (SP) tablet formulation. The study below compares the PK parameters of Paracetamol/calcium carbonate containing formulation and the standard paracetamol tablet, and to assesses their variability, since these can influence analgesic efficacy and response rates.

15

Methods:

A total of 76 healthy volunteers were recruited in an open-label, randomised, 8-way crossover study. Each formulation was administered in a replicate fashion, with a single
5 Ig dose taken 2 hours after a standard meal on 4 separate days. Blood samples were taken up to 10 hours after the initial dose and 4 hours after the replicate doses for pharmacokinetic (PK) analysis.

10 The primary objectives were: early exposure (rate of absorption, $AUC_{0-30 \text{ mins}}$, after both initial and replicate dosing), inter (between)-subject variation (inter-CV%, after initial dose) and intra-subject variation (intra-CV%, after replicate dosing). Secondary objectives included $AUC_{0-60 \text{ mins}}$, plasma concentration at 30 mins ($C_{pl \ 30 \text{ mins}}$) and percentage drug absorbed (PDA) at 30 and 60 minutes (measured by deconvolution analysis, variance measured for initial dose only).

15

Results:

$AUC_{0-30 \text{ mins}}$ for both the initial dose and after replicate dosing were very significantly higher for the Paracetamol/calcium carbonate containing formulation versus standard paracetamol formulation (initial dose: 0.98 versus 0.10 $\mu\text{g.h/ml}$ [median difference 0.77,
20 95% CI 0.53-1.01, $p < 0.0001$]; replicate dosing: 1.23 versus 0.15 $\mu\text{g.h/ml}$ [median difference 0.99, 95% CI 0.81-1.19, $p < 0.0001$]).

Inter-CV% for this parameter was significantly lower for the Paracetamol/calcium carbonate containing formulation versus standard paracetamol formulation (84.4% versus
25 192%, $p < 0.0001$).

Similarly, there was a significant difference for intra-CV% for $AUC_{0-30 \text{ mins}}$ (60.6% versus 116%, $p < 0.0001$). Similar reductions in inter-CV% and intra-CV% were observed for
30 $AUC_{0-60 \text{ mins}}$ and $C_{pl \ 30 \text{ mins}}$ along with inter-CV% for $PDA_{30 \text{ mins}}$ and $PDA_{60 \text{ mins}}$.

30

Conclusions:

These data clearly show that paracetamol absorption with the Paracetamol/calcium carbonate containing formulation is significantly faster than absorption with standard paracetamol formulation tablets. Importantly, paracetamol absorption with the
35 Paracetamol/calcium carbonate containing formulation also shows significantly less inter- and intra-subject variability. Taken together, these data have clear clinical implications in terms of a patient population obtaining rapid, and consistent, pain relief with this valuable

first-line pain therapy and therefore avoiding potential side effect issues with second-line treatments such as the NSAIDs.

EXAMPLE 3

5 DISINTEGRATION AND GASTRIC EMPTYING

Tablet disintegration and dissolution are key factors in in vivo speed of absorption and downstream pharmacokinetic parameters. Using the Paracetamol/calcium carbonate containing formulation an in vivo gamma scintigraphy investigation of tablet disintegration and gastric emptying (GE) was conducted.

10

Methods:

This single-dose, cross-over study involved 24 healthy volunteers. All participants ate a standard radio-labelled breakfast 2 hours (h) before taking the study medication (1 g paracetamol as either as Paracetamol/calcium carbonate containing formulation (described above) or a standard paracetamol tablet formulation described above (SP) [¹¹¹indium-DTPA-labelled tablet]).

15

The rate of disintegration was measured using gamma scintigraphy after defining the stomach area as the region of interest. Data were analysed using the WebLink[®] image analysis program. Onset and completion of tablet disintegration were determined by qualitative assessment of scintigraphic images. Tablet gastric emptying was determined by quantifying the amount of activity remaining in the stomach at a series of time points. Two parameters were used to assess GE: time to 50% emptying (T₅₀) and time to 90% emptying (T₉₀). Onset of GE was determined by qualitative assessment of scintigraphic images.

20
25

Results:

Both time to onset and completion of disintegration were significantly faster for the Paracetamol/calcium carbonate containing formulation than for the standard paracetamol formulation (6.4±4.3 versus 46.7±20.5 min, p<0.0001 and 12.9±26.4 versus 69.6±30.2 min, p<0.0001). Similarly, for GE, time to onset (41.9±28.8 versus 85.0±28.2, p<0.0001), T₅₀ (72.4±36.4 versus 100.7±30.6, p=0.0013) and T₉₀ (128.4±41.2 versus 142±33.8, p=0.10) were shorter for the Paracetamol/calcium carbonate containing formulation than for the standard paracetamol formulation. The time for GE of the standard meal did not differ between the Paracetamol/calcium carbonate containing formulation or the standard paracetamol formulation. Furthermore, while 75% of subjects taking the Paracetamol/calcium carbonate containing formulation showed onset of

30

35

16

disintegration/dissolution within 5 mins, none of the standard group exhibited onset at this time point.

Conclusions:

5 The Paracetamol/calcium carbonate containing formulation had a highly significant in vivo tablet disintegration advantage over the standard paracetamol formulation in this scintigraphy study. This correlates with enhanced GE for paracetamol with the Paracetamol/calcium carbonate containing formulation compared with standard paracetamol formulations.

10

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

15

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

20

What is Claimed Is:

1. A method for reducing inpatient variability in paracetamol containing formulations in patients having gastric dysmotility comprising administering to said
5 patient in need thereof, an orally administered pharmaceutical dosage form comprising a first active agent, calcium carbonate, at least one first binding agent, and at least one disintegrating agent as intragranular components in the form of a granulate, and as an extragranular component at least one hydrophilic colloid, an optionally a second binding agent, calcium carbonate, super disintegrant, and a second active agent.
10
2. The method according to Claim 1 wherein the patient is a diabetic patient.
3. The method according to Claims 1 or 2 wherein the first active agent is paracetamol, and wherein the optional extragranular agent comprises a second binding
15 agent present in an amount ranging from about 0.1% to about 10.0% by weight of the intragranular binding agent amount therein.
4. The method according to Claims 1 to 3 wherein the optional extragranular component comprises a second amount of calcium carbonate present in an amount
20 ranging from about 0.1% to about 10.0% by weight of the intragranular calcium carbonate amount therein.
5. The method according to Claims 1 to 4 wherein the optional extragranular component comprises a second active which is paracetamol present in an amount ranging
25 from about 0.1% to about 10.0% by weight of an intragranular first active agent which is paracetamol.
6. The method according to Claims 1 to 4 wherein the optional extragranular component comprises a super disintegrant present in an amount ranging from about 0.1%
30 to about 5.0% by weight of the composition.
7. The method according to Claims 1 to 6 wherein the hydrophilic colloid is selected from alginic acid, carageenan, gellan, pectin, agar or a combination of two or more thereof.
35
8. The method according to Claim 7 wherein the hydrophilic colloid comprises alginic acid.

9. The method according to any of Claims 1 to 8 wherein the hydrophilic colloid is present in an amount ranging from about 1.0% to about 5.0% by weight of the composition.

5

10. The method according to any of Claims 1 to 9 wherein the dosage form further comprises as an extragranular component a colorant, dye, flavorant, sweetener, lubricant, or glidant, or a combination of two or more thereof.

10

11. The method according to Claim 1 wherein the dosage form is a swallow tablet comprising paracetamol, calcium carbonate, pregelatinized starch, and any other optional intragranular components combined together in a granulation process to form a granulate, and then admixed with alginic acid and any other optional extragranular components to form a blend, and then compressed to form a tablet.

15

12. The method according to Claim 1 wherein the dosage form is a swallow tablet comprising a granulate containing as intragranular components paracetamol, calcium carbonate, and at least one binding agent which is microcrystalline cellulose or starch, and wherein the starch is selected from the group consisting of corn (maize) starch, modified corn starch, wheat starch, modified wheat starch, potato starch, pregelatinized starch or a combination of two or more starches thereof, with the proviso that if the binding agent comprises a mixture of corn (or maize) starch and pregelatinized starch then the weight ratio of pregelatinized starch to corn (or maize) starch is greater than from about 3.0 to 1.0; and optionally a disintegrating agent combined together in a granulation process to form a granulate; and containing as extragranular components a hydrophilic colloid selected from alginic acid, carageenan, gellan, pectin, agar or a combination of two or more thereof; and optionally at least one extragranular excipient which is a second active agent, a second amount of calcium carbonate, a second disintegrating agent, a second binding agent, a colorant, dye, flavorant, sweetener, lubricant, or glidant, or a combination of two or more thereof, and the components are compressed into a tablet.

30

13. The method according to Claim 12 wherein the hydrophilic colloid is alginic acid.

14. The method according to Claims 12 or 13 wherein the hydrophilic colloid is present in an amount ranging from about 1.0% to about 5.0% by weight of the composition.

35

15. The method according to Claim 12 wherein the granulate comprises a disintegrating agent which is a super disintegrant present in an amount ranging from about 0.5% to about 5.0% by weight of the composition.
- 5 16. The method according to Claim 12 wherein the intragranular binding agent is a pregelatinized starch.
17. The method according to Claim 16 wherein the starch is present in an amount ranging from about 5.0% to about 20.0% by weight of the composition.
- 10 18. The method according to Claim 12 wherein the binding agent comprises a first binding agent and a second binding agent, and wherein the first binding agent is starch.
19. The method according to Claim 18 where in the second binding agent is PVP.
- 15 20. The method according to any of Claims 1 to 19 wherein the intragranular active agent is paracetamol, and is present in an amount ranging from about 60.0% to about 80.0% by weight of the composition.
- 20 21. The method according to any of Claims 1 to 20 wherein the intragranular calcium carbonate is present in an amount ranging from about 5.0% to about 20.0% by weight of the composition.
22. The method according to any of Claims 1 to 20 wherein the intragranular calcium carbonate content in the granulate does not exceed 20.0% by weight of the composition.
- 25 23. A method for improving analgesia in a diabetic patient comprising administering to said patient in need thereof, an orally administered pharmaceutical dosage form comprising a first active agent, calcium carbonate, at least one first binding agent, and at least one disintegrating agent as intragranular components in the form of a granulate, and as an extragranular component at least one hydrophilic colloid, an optionally a second binding agent, calcium carbonate, super disintegrant, and a second active agent.
- 30 24. A method for improving absorption of paracetamol in a patient with gastric dysmotility comprising administering to said patient in need thereof, an orally administered pharmaceutical dosage form comprising a first active agent, calcium carbonate, at least one first binding agent, and at least one disintegrating agent as
- 35

intragranular components in the form of a granulate, and as an extragranular component at least one hydrophilic colloid, an optionally a second binding agent, calcium carbonate, super disintegrant, and a second active agent.

- 5 25. A method for improving analgesia in a diabetic patient comprising administering to said patient in need thereof, an orally administered pharmaceutical dosage form comprising
- 10 a) paracetamol;
- b) at least one agent which contributes to dissolution selected from sodium carbonate, ammonium carbonate, sodium bicarbonate, potassium bicarbonate, calcium carbonate, magnesium carbonate, disodium glycine carbonate, sodium glycine carbonate, lysine carbonate, arginine carbonate, or combinations of two or more of the above;
- 15 c) at least one water uptake agent selected from cross-linked polyvinylpyrrolidone (crospovidone), croscarmellose sodium, sodium starch glycolate, povidone, starch, starch derivatives, low substituted hydroxypropylcellulose, hydroxypropylcellulose, alginic acid, sodium alginate, calcium sulfate, calcium carboxymethylcellulose, microcrystalline cellulose, powdered cellulose, colloidal silicon dioxide, docusate sodium, guar gum, magnesium aluminum silicate,
- 20 methylcellulose, polacrilin potassium, silicified microcrystalline cellulose, magnesium oxide, tragacanth, mannitol, sorbitol, xylitol, sucrose, lactose, fructose, maltose, polyethylene glycol, amino acids, cyclodextrin, urea and/or polyvinylpyrrolidone; and
- 25 wherein at least 70 of the paracetamol is dissolved from the formulation within 180 seconds in USP dissolution apparatus 2 with 900ml of 0.05 N hydrochloric acid at 30 rpm and 37°C.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/52039

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/18, A61K 31/16 (2009.01)
USPC - 514/629

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHEDMinimum documentation searched (classification system followed by classification symbols)
USPC -- 514/629Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-- 424/400, 424/465, 424/692 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST -- PGPB,USPT,USOC,EPAB,JPAB; Dialog Classic Files ? 654, 652, 351, 349, 315, 6, 35, 65, 155; Google Scholar; USPTO Web Page; Search terms -- standardized dose, paracetamol, povidone, crospovidone, gastric dysmotility, diabetes, alginate acid, pregelatinized starch, binding agents, calcium carbonate, dissolution test**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0141144 A1 (ROBERTS et al.) 02 June 2007 (02.06.2007) para [0002], [0018], [0031], [0050], [0057], [0073], [0078], [0087]-[0088], [0101], [0138]-[0139], [0210],	1-3, 11-19, 23-25
Y	US 2004/0126318 A1 (EPHREPREIS) 01 July 2004 (01.07.2004) para [0003], [0017]-[0019], [0035]-[0036], [0038]-[0039], [0065], [0078], [0085]-[0086]	1-3, 11-19, 23-25
Y	US 2004/0170681 A1 (GRATTAN) 02 September 2004 (02.09.2004) para [0001], [0011], [0016], [0021], [0035], [0037]	3, 11-19

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 2009 (10.09.2009)

Date of mailing of the international search report

22 SEP 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/52039

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-10 and 20-22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

MÉTODO NOVEDOSO

CAMPO DE LA INVENCION

5 La presente invención está dirigida a métodos novedosos de uso para formulaciones que contienen paracetamol que proveen una rápida disolución del agente activo seguido de absorción mejorada en pacientes con vaciamiento gástrico retardado.

10

ANTECEDENTES DE LA INVENCION

La presente invención es el uso de una formulación de paracetamol que se ha demostrado de manera inesperada que tiene perfiles farmacocinéticos mejorados en pacientes que tienen dismotilidad gástrica o
15 gastroparesis. Históricamente, se ha demostrado que la diabetes reduce la motilidad gástrica (gastroparesis) en hasta 50% en pacientes en comparación con individuos no diabéticos.

La participación del sistema nervioso autónomo en pacientes que tienen diabetes mellitus incluye enteropatía gástrica caracterizada por
20 dismotilidad gastrointestinal. Bassotti, G., Recenti Prog Med. 82: 334-337 (1991). La diabetes mellitus de muchos años puede reducir el vaciamiento gástrico en hasta 50% de los pacientes. O'Mahony et al., Drugs Aging, 19: 515-527 (2002). El impacto de diversas enfermedades relacionadas con la

edad en la motilidad gastrointestinal en las personas mayores puede incluir también aquellos pacientes con depresión que prolonga de manera significativa el tiempo de tránsito por todo el intestino; hipotiroidismo, falla renal crónica y enfermedad de Parkinson idiopática. Con frecuencia los
5 fármacos en las personas mayores pueden causar motilidad gastrointestinal desordenada, tal como anticolinérgicos, analgésicos opioides y antagonistas del calcio.

La importancia de la dismotilidad en pacientes, en particular las personas mayores, puede resultar en consecuencias clínicas graves donde la
10 respuesta clínica a un medicamento es retardada, tal como en la absorción de levodopa retardada o con diuréticos. Como los opioides y anticolinérgicos ya tienen efectos inhibitorios en el vaciamiento gástrico, esto puede retardar la absorción de otros fármacos. Por consiguiente, la necesidad de una
variabilidad intrapaciente consistente y baja en la absorción de fármacos, tales
15 como analgésicos, en dicha población de pacientes es muy grande.

BREVE DESCRIPCIÓN DE LA INVENCION

La presente invención está dirigida a un método novedoso para
20 reducir la variabilidad intrapaciente en un agente farmacéuticamente activo que de manera adecuada no se absorbe en el estómago, tal como formulaciones que contienen paracetamol en pacientes que tienen dismotilidad gástrica, y la presente invención está dirigida a un método para

mejorar la analgesia en un paciente diabético, o para mejorar la absorción de un agente activo en un paciente con dismotilidad gástrica, todos estos métodos comprenden administrar oralmente a un paciente que lo necesita, una forma de dosificación farmacéutica que comprende un primer agente activo, de manera adecuada paracetamol, carbonato de calcio, al menos un primer agente aglutinante, y al menos un agente desintegrante como componentes intragranulares en forma de un material granulado, y como un componente extragranular al menos un coloide hidrofílico, opcionalmente un segundo agente aglutinante, carbonato de calcio, un superdesintegrante, y un segundo agente activo.

DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención está dirigida a un método novedoso para mejorar la variabilidad de absorción de un agente activo entre pacientes que tienen dismotilidad gástrica. La dismotilidad gástrica es conocida también como hipomotilidad gástrica. La hipomotilidad gástrica, en pacientes por lo demás normales, puede ser inducida por una variedad de factores ambientales, farmacológicos y fisiológicos. De manera importante, el vaciamiento gástrico retardado puede tener un efecto dañino en la absorción de fármacos tales como paracetamol, los cuales se absorben principalmente en el intestino delgado. Esto puede dar por resultado niveles en plasma retardados e inconsistentes de un medicamento, y puede causar incomodidad

cuando el medicamento particular es un medicamento para el dolor tal como paracetamol.

Para propósitos de la presente el agente activo es de manera adecuada ninguno que sea absorbido en el estómago. Se pretende que la presente formulación introduzca el agente activo en el duodeno a un índice incrementado con respecto a una formulación de otro modo estándar del agente activo. Por lo tanto, se espera que cualquier principio activo que sea absorbido principalmente después del esfínter pilórico (por ejemplo, en la parte inferior del estómago) en vez de en el estómago en sí muestre un perfil farmacocinético más rápido y más consistente. Como se describirá en la presente en mayor detalle, el agente activo, paracetamol ha sido elegido en la presente para describir la invención. Se ha demostrado que el paracetamol en una forma de dosificación estándar no contribuye al índice de vaciamiento del fármaco desde el estómago.

El paracetamol es un fármaco analgésico y antipirético efectivo en el alivio del dolor leve a moderado. La dosis terapéutica recomendada en el Reino Unido es 500-1000 miligramos (mg) cada 4 a 6 horas (hr) hasta un máximo de 4000 mg diario. La biodisponibilidad oral absoluta es aproximadamente 80% y es independiente de la dosis en el rango de 5-20 mg/kg. Los niveles en plasma máximos se obtienen entre 0.5 y 3 horas después de la dosis dependiendo de la formulación.

El paracetamol tiene una vida media en plasma promedio de 2.4 horas en adultos con un rango de 1.5-3.0 horas. Varía relativamente poco

entre individuos, y no se prolonga a un grado clínicamente significativo en los extremos de edad. No se une a la proteína del plasma a ningún grado y el volumen de distribución es aproximadamente 0.9 litros/kilogramo (l/kg) de peso corporal.

5 El paracetamol oral es principalmente absorbido desde el intestino delgado superior y para formulaciones en tableta de dosis sólida estándar el índice de absorción es limitado por i) el proceso de desintegración/disolución de la tableta y ii) vaciamiento gástrico desde el estómago al intestino delgado superior.

10 La diabetes mellitus (tipo 2) es la causa más común de motilidad gastrointestinal dañada en las personas mayores. El vaciamiento gástrico puede ser anormal en esta población y, por lo tanto, impactar en el perfil de absorción del agente activo, tal como paracetamol. La presente invención ha investigado el perfil de absorción del paracetamol desde una forma de dosificación estándar y desde una forma de dosificación granulada de paracetamol y carbonato de calcio, y ha determinado que la diferencia relativa en los perfiles de absorción observados en voluntarios sanos es cambiada al usar pacientes diabéticos como un modelo de dismotilidad gástrica.

20 Una modalidad de la presente invención está dirigida al uso de una composición granulada de paracetamol como se describirá aún más en la presente, que ahora se ha demostrado que provee una absorción significativamente mayor a los 30 minutos, y que tiene niveles en plasma Cmax estadísticamente significativos a los 30 minutos con respecto a las

formulaciones que contienen paracetamol estándar en pacientes que tienen dismotilidad gástrica. En una modalidad de la invención, los pacientes que tienen dismotilidad gástrica son pacientes diabéticos.

También se ha demostrado que la presente invención provee
5 una absorción significativamente mayor a los 60 minutos con respecto a formulaciones que contienen paracetamol estándar en pacientes que tienen dismotilidad gástrica.

No obstante, aunque se ha demostrado también que la presente invención tiene un tiempo más corto hasta la concentración máxima (T_{max}) en
10 comparación con paracetamol estándar, la diferencia no fue estadísticamente significativa. En conjunto la población diabética muestra una absorción más lenta de paracetamol a partir de ambos tratamientos cuando se compara con los resultados observados en voluntarios sanos y esto se podría atribuir en
15 lo tanto, los pacientes con diabetes tipo 2 son un modelo de dismotilidad adecuado que se puede usar para evaluar el perfil PK del paracetamol a partir de dos formulaciones diferentes.

La forma de dosificación que contiene paracetamol comprende paracetamol, carbonato de calcio, al menos un agente aglutinante, y al menos
20 un agente desintegrante, como componentes intragranulares en forma de un material granulado, y como un componente extragranular, un coloide hidrofílico, opcionalmente un agente aglutinante, carbonato de calcio, un superdesintegrante, y/o paracetamol adicional. Una fórmula que contiene

13

dichos excipientes ha sido descrita en WO 2007/118063, presentada el 3 de abril de 2007, cuya descripción se incorpora como referencia en la presente en su totalidad.

Aunque no se desea limitar a dicha forma de dosificación, se cree también que las formas de dosificación que contienen paracetamol como se describen en Roberts et al., US 2007/0141144, publicada el 21 de junio de 2007 o una publicación WO anterior pero relacionada, WO 2005/15344, publicada el 8 de diciembre de 2005, cuyas descripciones se incorporan en la presente como referencia, también son aceptables para usar en los métodos aquí descritos.

Una composición de liberación rápida de acuerdo con esta invención se desintegra y disuelve rápidamente en el estómago para facilitar la rápida absorción del agente activo en el sistema circulatorio. Para propósitos de la presente, "liberación rápida" significa en donde al menos 60% del principio activo se ha disuelto de la composición a los 180 segundos, como se determina mediante el método de prueba de disolución aquí descrito. En otra modalidad, de manera adecuada al menos 70% del principio activo se ha disuelto. En otra modalidad al menos 80% se ha disuelto, y en otra modalidad al menos 90% del agente activo se ha disuelto de la composición a los 180 segundos. Un método de prueba de disolución adecuado para este propósito utiliza las mismas condiciones que se describen en WO 02/100391, es decir un aparato de paletas USP que rota a 30 rpm, que emplea 900 ml de HCl 0.05 M a 37°C como el medio de disolución. En esta referencia, el porcentaje de

paracetamol disuelto se determinó a los quince minutos, en lugar de los 180 segundos como se describe en US 2007/0141144. Asimismo se mencionan como adecuados los métodos de disolución descritos a los 5, 10, 15, 20, 25, y 30 minutos en Rostami-Hodjegan et al., Drug Development and Industrial
5 Pharmacy, 28(5), pp 533-5439 (2002).

Aunque índices de liberación de paracetamol se han determinado para muchos productos de paracetamol disponibles comercialmente y se ha encontrado que varían de aproximadamente 12% a aproximadamente 32%, una liberación rápida del principio activo es solamente
10 parte de la presente invención. No sólo el principio activo debe ser liberado de su forma de dosificación, el principio activo también debe ser vaciado del estómago al duodeno a un índice que sea consistente de paciente a paciente, y en particular en pacientes con motilidad gástrica reducida debe ser vaciado tan cerca de lo normal como sea posible.

15 Por consiguiente, un aspecto de la invención provee una composición farmacéutica que comprende un principio activo, carbonato de calcio, al menos un agente aglutinante, y al menos un agente desintegrante, como componentes intragranulares en la forma de un material granulado.

El material granulado se puede combinar opcionalmente con uno
20 o más componentes extragranulares adecuados, y puede estar en forma de una "tableta" la cual puede incluir tableta de cualquier forma, e incluye comprimidos ovalados, los cuales son tabletas que tienen forma de cápsula.

24

La formulación puede ser colocada en cápsulas, o puede estar disponible en bolsitas de dosis unitarias.

Cuando está en una forma de dosificación unitaria, una composición de acuerdo con la invención comprende una cantidad terapéuticamente efectiva del principio activo. En una modalidad el principio activo es paracetamol, por lo cual se entiende una cantidad de paracetamol suficiente para obtener un beneficio terapéutico. De manera adecuada, dicha cantidad se encuentra en el rango de 250 mg a 1000 mg por forma de dosificación unitaria (por ejemplo, por tableta) y típicamente es ya sea 325 mg o 500 mg.

Aunque el principio activo está presente como un componente intragranular, se reconoce que una cantidad ilimitada del mismo o de un principio activo diferente también puede estar presente en forma extragranular. Aunque no se ha preparado y sometido a prueba, otra modalidad de la invención incluye una formulación en donde el agente activo es únicamente dispersado en la formulación como un componente extragranular.

Una composición farmacéutica de acuerdo con la invención comprende carbonato de calcio intragranular. De manera apropiada el contenido de carbonato de calcio en el material granulado no excede de 20.0% en peso de la composición, y, por ejemplo, en una modalidad está presente en una cantidad de aproximadamente 5.0% a aproximadamente 20.0% en peso, de manera adecuada de aproximadamente 5.0% a

aproximadamente 15.0% en peso de la composición. En una modalidad alternativa el contenido de carbonato de calcio es de aproximadamente 8.0% a aproximadamente 15.0% en peso de la composición.

En una modalidad de acuerdo con la invención el contenido de paracetamol en el material granulado se encuentra en el rango de 70.0 a 80.0% en peso de la composición y el carbonato de calcio en el material granulado se encuentra en el rango de 8.0% a 15.0% en peso de la composición. Por ejemplo, una composición de paracetamol de 500 mg puede comprender 30 mg a 110 mg de carbonato de calcio intragranular, y una composición de paracetamol de 325 mg puede comprender 20 mg a 72 mg de carbonato de calcio intragranular.

Aunque el carbonato de calcio está presente como un componente intragranular, se reconoce que una cantidad limitada de carbonato de calcio, por ejemplo, hasta aproximadamente un 25.0% en peso adicional del contenido de carbonato de calcio intragranular de la composición, puede estar también presente en forma extragranular. En una modalidad una composición de acuerdo con la invención comprende, como un componente extragranular, carbonato de calcio en una cantidad que varía de aproximadamente 0.1% a aproximadamente 10.0% en peso de la cantidad de carbonato de calcio intragranular en la misma.

Una composición de acuerdo con la invención comprende en forma intragranular, un componente que funciona como un aglutinante, tal como uno o más agentes aglutinantes. De manera apropiada el agente

aglutinante puede comprender un primer agente aglutinante y un segundo agente aglutinante. Agentes aglutinantes adecuados para usar en la presente incluyen agentes aglutinantes convencionales usados en la técnica tales como almidones, polímeros y derivados de celulosa o combinaciones de los mismos.

Si el agente aglutinante incluye un almidón, de manera adecuada es de origen vegetal tal como almidón de maíz, almidón de maíz modificado, almidón de trigo, almidón de trigo modificado, almidón de papa, o almidón pregelatinizado, por ejemplo, disponible comercialmente como Almidón 1500 G o Prejel; o una combinación de dos o más de los mismos.

Combinaciones de almidón con otros agentes aglutinantes, tal como los que se describen en la presente, se contemplan también dentro del alcance de la invención. En una modalidad, de manera apropiada el almidón es almidón pregelatinizado, donde es el único o un primer agente aglutinante.

El almidón pregelatinizado es un almidón que ha sido química y/o mecánicamente procesado. Típicamente, el almidón pregelatinizado comprende 5% de amilasa libre, 15% de amilopectina libre, y 80% de almidón sin modificar. El almidón pregelatinizado se puede obtener de almidón de maíz, papa o arroz. Se ha encontrado que el índice de disolución del paracetamol es afectado de manera adversa en una composición que comprende como componentes intragranulares: paracetamol, carbonato de calcio, almidón de maíz, almidón pregelatinizado, Povidona K25 y sorbato de potasio, en donde la relación en peso de almidón pregelatinizado a almidón de

maíz es aproximadamente 2.3:1. Por consiguiente, si el agente aglutinante comprende una mezcla de almidón de maíz y almidón pregelatinizado, entonces la relación en peso de almidón pregelatinizado a almidón de maíz es al menos 3.0:1.0. En una modalidad de esta invención, la relación en peso de almidón pregelatinizado a almidón de maíz es al menos 5.0:1.0.

De manera apropiada, cuando se encuentra presente en una composición de la invención, el almidón está presente en el material granulado en una cantidad de aproximadamente 1.0% a aproximadamente 30.0% en peso de la composición, típicamente de aproximadamente 5.0% a aproximadamente 20.0%, por ejemplo, de aproximadamente 8.0% a aproximadamente 15.0% en peso de la composición.

Si el agente aglutinante incluye un polímero, de manera adecuada es polivinilpirrolidona o povidona (PVP), alcohol polivinílico (PVA), óxido de polietileno, polaxámero, polimetacrilato, por ejemplo, un carbómero, polietilenglicol (PEG) tal como PEG 3350 y policarbófilo de calcio; o una combinación de dos o más de los mismos. Combinaciones de un polímero con otros agentes aglutinantes, tales como aquellos que se describen en la presente, también están contemplados dentro del alcance de la invención. Cuando el polímero comprende PVP, de manera adecuada comprenderá un peso molecular de aproximadamente 30,000, por ejemplo, disponible comercialmente como PVP K25. De manera apropiada, cuando se encuentra presente en una composición de la invención, el polímero está presente en el material granulado en una cantidad de aproximadamente 1.0% a

26

aproximadamente 10.0% en peso de la composición, típicamente de aproximadamente 1.5% a aproximadamente 5.0% en peso de la composición.

En una modalidad, un polímero tal como PVP está presente como un segundo agente aglutinante. En una modalidad un almidón tal como almidón pregelatinizado está presente como un primer agente aglutinante, en una cantidad que varía de aproximadamente 10.0% a aproximadamente 15.0% en peso de la composición, y un polímero tal como PVP está presente como un segundo agente aglutinante en una cantidad que varía de aproximadamente 1.5% a aproximadamente 5.0% en peso de la composición.

10 De manera adecuada dicha modalidad está sustancialmente libre de almidón de maíz, por ejemplo, comprendiendo no más de una cantidad que varía de entre aproximadamente 0.0% a aproximadamente 1.0% de almidón de maíz.

Si el agente aglutinante incluye un derivado celulósico, de manera apropiada incluye al menos uno de hidroxipropilcelulosa (HPC) (versiones de viscosidad baja a media de la misma), por ejemplo, como puede estar disponible comercialmente bajo el nombre comercial Klucel® de la división Aqualon de Hercules Inc., Dow Chemical Company, por ejemplo, Klucel GF, Klucel JF, Klucel LF y Klucel EF; hidroxipropilmetilcelulosa (HPMC) (versiones de viscosidad baja a media de la misma), por ejemplo, como puede estar disponible comercialmente bajo el nombre comercial Methocel® de la Dow Chemical Company, por ejemplo, Methocel E15Premium, Methocel E3Premium LV, Methocel K100LV; celulosa microcristalina (MCC), carboximetilcelulosa (MC), carboximetiletilcelulosa de sodio; o una

combinación de dos o más de los mismos. Combinaciones de un derivado celulósico con otros agentes aglutinantes antes mencionados se contemplan también dentro del alcance de la invención.

El término viscosidad "baja a media" como se usa en la presente
5 significa una viscosidad en el rango de aproximadamente 15 a
aproximadamente 1000 mPa.s. Se reconoce en la técnica que la
determinación de la viscosidad de derivados celulósicos se basa en técnicas y
clasificación estándar en la técnica, por ejemplo, para HPMC, la viscosidad se
puede determinar a 20°C con una solución al 2% usando un viscosímetro
10 Ubbelohde, o para HPC, la viscosidad se puede determinar a 25°C con una
solución al 2-10% usando un viscosímetro LVF Brookfield. En general el
derivado celulósico está presente en el material granulado en una cantidad
que varía de aproximadamente 0.5% a aproximadamente 5.0% en peso de la
composición. Se reconoce en la técnica que ciertos derivados celulósicos,
15 tales como HPMC, tendrán diversos roles en una formulación, dependiendo
de la cantidad usada. Por ejemplo, HPMC (de viscosidad baja o media) puede
funcionar como un agente aglutinante, un agente de revestimiento, o como un
agente formador de matriz. Se ha encontrado que cuando HPMC (de
viscosidad baja o media) se usa a aproximadamente 10.0% en peso de la
20 composición, el índice de disolución del paracetamol es retrasado,
probablemente debido a las propiedades de liberación extendida de HPMC.
De acuerdo con la presente invención, cuando se usa como un agente
aglutinante, la HPMC está presente en una cantidad típicamente no más de

2.5% en peso de la composición, por ejemplo, en una cantidad de aproximadamente 1.0% a aproximadamente 2.5% en peso de la composición.

La cantidad total de agente aglutinante presente en forma intragranular en una composición de acuerdo con la invención es de manera adecuada en una cantidad que varía de aproximadamente 1.0% a aproximadamente 30.0% en peso de la composición, por ejemplo, de aproximadamente 2.0% a aproximadamente 25.0% en peso de la composición, o de manera alternativa de aproximadamente 5.0% a aproximadamente 20.0% en peso de la composición.

10 Aunque un agente aglutinante está presente como un componente intragranular, se reconoce que una cantidad modesta de agente aglutinante, por ejemplo, hasta aproximadamente un 5.0%-10.0% en peso adicional del contenido de agente aglutinante intragranular de la composición, puede también estar presente en forma extragranular. En una modalidad una
15 composición de acuerdo con la invención comprende, como un componente extragranular, un agente aglutinante en una cantidad que varía de aproximadamente 0.1% a aproximadamente 10.0% en peso de la cantidad de agente aglutinante intragranular en la misma.

Una composición de acuerdo con la invención comprende, como
20 un componente intragranular, al menos un componente que funciona como un desintegrante, y puede incluir al menos dos agentes desintegrantes. Agentes desintegrantes adecuados incluyen un agente no superdesintegrante, un superdesintegrante o una combinación de ambos. Agentes no

superdesintegrantes adecuados incluyen desintegrantes convencionales tales como almidón (de maíz), almidón pregelatinizado, por ejemplo, almidón 1500 G, arcillas (Veegum o Bentonita), celulosa microcristalina, celulosa o celulosa en polvo. Se reconoce en la técnica que algunos excipientes pueden realizar

5 más de un papel en una formulación farmacéutica dada. Por ejemplo, ciertos excipientes, por ejemplo, almidones incluyendo almidón pregelatinizado, y celulosa microcristalina (anteriormente identificados como agentes aglutinantes) funcionan como aglutinantes y desintegrantes a la vez. Por consiguiente, se entenderá que el mismo excipiente puede actuar como un

10 agente aglutinante y como un agente desintegrante a la vez. En dichos casos, la inclusión de un agente desintegrante además de un agente aglutinante es completamente opcional. Igualmente, en tales casos, la inclusión de un agente aglutinante además de un agente desintegrante es totalmente opcional.

Una modalidad de la invención provee como componentes

15 intragranulares, paracetamol y carbonato de calcio, y al menos un agente aglutinante que es celulosa microcristalina o almidón, en donde el almidón es almidón de maíz, almidón de maíz modificado, almidón de trigo, almidón de trigo modificado, almidón de papa, almidón pregelatinizado o una combinación de dos o más almidones de los mismos, con la condición de que si el agente

20 aglutinante comprende una mezcla de almidón de maíz y almidón pregelatinizado entonces la relación en peso de almidón pregelatinizado a almidón de maíz es mayor que de aproximadamente 3.0 a 1.0; y de manera

opcional un agente desintegrante; y uno o más ingredientes farmacéuticamente aceptables como componentes extragranulares.

Las composiciones en la presente pueden incluir un agente no superdesintegrante que puede estar presente en forma intragranular, extragranular o en forma tanto intragranular como extragranular. Cuando un agente no superdesintegrante se encuentra ya sea ausente de la composición o está presente sólo en forma extragranular, el agente desintegrante comprenderá de manera adecuada un superdesintegrante, presente en forma intragranular.

De manera apropiada un agente no superdesintegrante estará presente en forma intragranular en una cantidad que varía de aproximadamente 5.0% a aproximadamente 30.0% en peso de la composición, de manera adecuada de aproximadamente 5.0% a aproximadamente 20.0% en peso de la composición. Cuando está presente en forma extragranular, el agente no superdesintegrante puede estar también presente en una cantidad, por ejemplo, hasta aproximadamente un 5.0%-10.0% en peso adicional del contenido de agente no superdesintegrante intragranular de la composición.

Un superdesintegrante, si se usa, puede estar presente en forma intragranular, extragranular o tanto en forma intragranular como extragranular. Se reconoce que cuando un superdesintegrante está ya sea ausente de la composición o está presente sólo en forma extragranular, el agente desintegrante comprenderá un agente no superdesintegrante, presente en

forma intragranular. Un superdesintegrante se puede usar en forma intragranular o extragranular, en una cantidad que varía de aproximadamente 0.5% a aproximadamente 5.0% en peso de la composición. La cantidad total de superdesintegrante puede estar en una cantidad que varía de aproximadamente 0.5% a aproximadamente 10.0% en peso de la composición.

Los "superdesintegrantes" representan una clase de agente desintegrante que en general se puede usar en cantidades más bajas en preparaciones farmacéuticas, en comparación con desintegrantes convencionales. Ejemplos de superdesintegrantes incluyen glicolato de almidón de sodio, la sal de sodio de almidón de carboximetilo, celulosa modificada y polivinilpirrolidona entrelazada. El glicolato de almidón de sodio se encuentra disponible comercialmente bajo los nombres comerciales Explotab® (Edward Mendell Co.), Primojel® (Generichem Corp) y Tablo® (Blanver, Brasil). Un ejemplo de celulosa modificada incluye croscarmelosa, la sal de sodio de carboximetilcelulosa. La croscarmelosa está disponible comercialmente bajo los nombres comerciales AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Los Países Bajos), Primellose® (Avebe, Los Países Bajos), Solutab® (Blanver, Brasil). Un ejemplo de una polivinilpirrolidona entrelazada incluye crospovidona, y se encuentra disponible comercialmente bajo los nombres comerciales Kollidon CL® o Kollidon CL-M (BASF Corp.), y Polyplasdone XL® (ISP Corp). De manera adecuada el agente desintegrante comprende polivinilpirrolidona entrelazada.

29

Una composición de acuerdo con la invención puede contener de manera opcional otros componentes extragranulares farmacéuticamente aceptables adicionales. Por ejemplo, una composición de acuerdo con la invención puede comprender un coloide hidrofílico tal como ácido algínico, carragenina, gelatina, pectina y/o agar, como un componente extragranular. De manera apropiada el coloide hidrofílico es ácido algínico. Cuando se encuentra presente, un coloide hidrofílico está presente en una cantidad que varía de aproximadamente 1.0% a aproximadamente 5.0% en peso de la composición.

10 En un aspecto una composición de acuerdo con la invención comprende ácido algínico como un componente extragranular.

Otros componentes extragranulares farmacéuticamente aceptables incluyen, mas no se limitan a, un agente antimicrobiano, por ejemplo, sorbato de potasio o un parabeno, es decir, uno o más ésteres de ácido hidroxibenzoico, por ejemplo, metilo, etilo, propilo o butilo, de manera adecuada en forma individual o como mezclas. En una modalidad de la invención se usa un parabeno.

En una modalidad la composición comprende paracetamol, carbonato de calcio, almidón pregelatinizado, y povidona como componentes intragranulares, y como componentes extragranulares ácido algínico y crospovidona, y de manera opcional otros componentes extragranulares, de preferencia comprimidos en una tableta. De manera apropiada, el ácido

20

algínico está presente en una cantidad que varía de aproximadamente 1.0% a aproximadamente 5.0% en peso de la composición.

Componentes extragranulares farmacéuticamente aceptables adicionales incluyen un tinte; colorante; saborizante; auxiliar de compresión; 5 conservador; agente humectante; agente formador de cuerpo; adhesivo; agente edulcorante; lubricante tal como estearato de magnesio, estearato de calcio, estearato de sodio, ácido esteárico o talco; y un auxiliar de flujo o agente resbalador tal como dióxido de silicio coloidal (Cab-O-Sil, Syloid™). De manera adecuada, cuando está presente, un lubricante o auxiliar de flujo se 10 usa cada uno en una cantidad que varía de 0.1% a 5.0% en peso de la composición. Se reconoce que componentes farmacéuticamente aceptables adicionales pueden estar presentes como componentes intragranulares así como componentes extragranulares.

Además de paracetamol, las composiciones de la invención 15 pueden contener también otros agentes farmacéuticamente activos, por ejemplo, a otros analgésicos tales como codeína, hidrocodona, oxicodona, tramadol y propoxifeno; analgésicos antiinflamatorios tales como NSAIDs, por ejemplo, aspirina e ibuprofeno; descongestionantes tales como pseudoefedrina y fenilefrina; antitusivos tales como folcodina y dextrometorfano; 20 expectorantes tales como guaifenesina y bromhexina; diuréticos tales como pamabrom; antihistaminas sedantes y no sedantes tales como difenhidramina, doxilamina y mepiramina; agentes gastrointestinales tales como metoclopramida; triptanos tales como sumatriptano; y relajantes musculares

tales como metocarbamol; y adyuvantes, por ejemplo, cafeína. Como se mencionó anteriormente, agentes farmacéuticamente activos y adyuvantes pueden estar presentes en forma intragranular, extragranular o tanto intragranular como extragranular.

5 En otro aspecto se provee una composición que comprende cafeína en forma intragranular, extragranular o tanto intragranular como extragranular. De manera apropiada la cafeína está presente en forma extragranular. En una modalidad la cafeína está además de una formulación que contiene paracetamol intragranular.

10 Como se usa en la presente el término "agente farmacéuticamente activo" incluye, mas no se limita a, fármacos, suplementos dietarios, vitaminas, minerales, nutracéuticos y agentes veterinarios. Este término incluye agentes bioactivos, agentes activos, agentes terapéuticos, o fármacos como se definen en la presente, y sigue los lineamientos de la Guía
15 de La Unión Europea para La Buena Práctica de Manufactura. Se pretende que dichas sustancias provean actividad farmacológica u otro efecto directo en la cura, mitigación, tratamiento o prevención de enfermedades o afecten la estructura y función del cuerpo. La actividad farmacológica puede ser profiláctica, o para tratamiento de un estado de enfermedad.

20 Los fármacos incluyen aquellos destinados para administración oral. Una descripción de estas clases de fármacos y un listado de especies dentro de cada clase se pueden encontrar en Martindale, The Extra Pharmacopoeia, Twenty-ninth Edition, The Pharmaceutical Press, Londres,

1989. Los fármacos se encuentran comercialmente disponibles y/o se pueden preparar por medio de técnicas conocidas en la técnica.

La invención se describirá ahora como referencia a los siguientes ejemplos biológicos los cuales son meramente ilustrativos y no se deben
5 interpretar como una limitación del alcance de la presente invención.

EJEMPLO 1

Perfil farmacocinético en pacientes con dismotilidad gástrica

10 La diabetes de muchos años puede haber reducido la motilidad gástrica en hasta 50%. Por lo tanto, los pacientes con diabetes tipo 2 fueron elegidos como un modelo de dismotilidad para evaluar el perfil PK del paracetamol a partir de dos formulaciones diferentes. Este estudio fue un estudio PK de un solo centro, de dos vías, de etiqueta abierta, al azar, de una
15 sola dosis, cruzado. Los sujetos recibieron una sola dosis oral de 1 gm de una formulación de la invención o formulación de paracetamol estándar, 2 horas después de una comida estándar, con pacientes asignados al azar con un reposo farmacológico de 24 horas entre la dosificación. 21 pacientes completaron el protocolo, 18 masculinos y 3 femeninos. Se tomaron muestras
20 de sangre 4 horas después de la dosis para análisis farmacocinéticos.

El objetivo del estudio primario fue comparar la exposición temprana, como se evaluó por medio de índice de absorción (área bajo la curva [AUC]_{0-30 mins}). Otras variables de exposición temprana incluyeron tiempo

31

hasta la concentración máxima (T_{max}), y variabilidad inter-paciente (coeficiente de variación (CV)) en $AUC_{0-30\text{ mins}}$, $AUC_{0-60\text{ mins}}$ y concentración en plasma (C_{plasma}) a los 30 minutos.

Tabletas de Panadol estándar son tabletas revestidas con una película que contienen 500 mg de paracetamol, y contienen como excipientes, almidón pregelatinizado, almidón de maíz, talco, ácido esteárico, povidona, sorbato de potasio, hipromelosa y triacetato de glicerol. ; .

La formulación de carbonato de calcio/paracetamol usada en la presente contiene 500 mg de paracetamol y es similar a la que se describe en el ejemplo 6 de WO 2007/118063.

Resultados

15	Parámetro	Fórmula de paracetamol/ carbonato de calcio (n=21) Media, mediana, CV%	Panadol Estándar (n=21) Media, mediana, CV%	Diferencia de medianas	Valor p (prueba de Wilcoxon)	Valor p (prueba de rangos cuadrados CV)
	$AUC_{0-30min}$ (ug/ml.h)	0.45, 0.28, 153.1	0.14, 0.04, 215.8	0.18	0.0004	0.0522
20	$AUC_{0-60min}$ (ug/ml.h)	2.10, 1.38, 102.8	0.84, 0.26, 174.9	1.02	0.0014	0.0801
	C_{plasma} a los 30 mins (ug/ml)	2.48, 1.52, 125.0	0.84, 0.19, 282.7	1.08	0.0002	0.0693

5

Parámetro	Fórmula de paracetamol/ carbonato de calcio (n=21) Media, mediana, CV%	Panadol Estándar (n=21) Media, mediana, CV%	Diferencia de medianas	Valor p (prueba de Wilcoxon)	Valor p (prueba de rangos cuadrados CV)
Tmax (h)	2.36, 2.50, 41.4	2.77, 2.75, 33.5	-0.25	0.1448	-
Cmax (ug/ml)	8.99, 7.97, 34.9	9.49, 9.77, 28.9	-	-	-
AUC0-tmin (ug/ml.h)	21.01, 18.92, 35.1	18.5, 16.04, 7.9	-	-	-

10

AUC₀₋₃₀ min (objetivo primario) fue estadísticamente y de manera significativa mayor para la formulación que contiene paracetamol/carbonato de calcio que para el paracetamol estándar (p=0.0004).

15 AUC₀₋₆₀ min y Cplasma a los 30 minutos fue estadísticamente y de manera significativa mayor (p=0.0014) y más alta (p=0.0002), respectivamente, para la formulación que contiene paracetamol/carbonato de calcio en comparación con el paracetamol estándar.

20 El tiempo hasta la concentración máxima (Tmax) fue más corto para la formulación que contiene paracetamol/carbonato de calcio en comparación con paracetamol estándar pero la diferencia no fue estadísticamente significativa (p=0.1448).

Hubo una tendencia hacia la importancia estadística para la comparación de CVs para AUC₀₋₃₀ min (p=0.0522), AUC₀₋₆₀ min (p=0.0801) y

32

Cplasma a los 30 minutos ($p=0.0693$) en favor de la formulación que contiene paracetamol/carbonato de calcio.

La formulación que contiene paracetamol/carbonato de calcio fue absorbida más rápidamente que las tabletas de paracetamol estándar, y
5 demostró una tendencia hacia menos variabilidad inter-paciente (con base en el coeficiente de variación) en esta población de pacientes diabéticos.

El tamaño de muestra planeado fue menor que lo deseado, y puede explicar por qué hubo una falta de importancia estadística para la comparación de T_{max} obtenida. En conjunto la población sometida a prueba
10 (diabéticos) en este estudio mostró una absorción más lenta de paracetamol de ambos tratamientos cuando se compara con los resultados observados en voluntarios sanos y esto se podría atribuir en parte a la enteropatía gástrica que se sabe ocurre en la diabetes mellitus. No obstante, la formulación que contiene paracetamol/carbonato de calcio parece mantener las ventajas de la
15 absorción rápida y consistente demostrada en voluntarios previamente sanos, aún en aquellos pacientes con diabetes mellitus.

EJEMPLO 2

Estudio de parámetros farmacocinéticos

20

Previamente se había determinado en un estudio clínico que la formulación que contiene paracetamol/carbonato de calcio (como se describe anteriormente) es vaciada del estómago más rápidamente que una

formulación de tableta de paracetamol estándar (SP). El estudio a continuación compara los parámetros PK de la formulación que contiene paracetamol/carbonato de calcio y la tableta de paracetamol estándar, para evaluar su variabilidad, ya que éstos pueden influenciar la eficacia analgésica e índices de respuesta.

Métodos

Un total de 76 voluntarios sanos fueron reclutados en un estudio de etiqueta abierta, aleatorio, de 8 vías cruzado. Cada formulación fue administrada en forma repetida, con una sola dosis de 1 g tomada 2 horas después de una comida normal en 4 días separados. Se tomaron muestras de sangre hasta 10 horas después de la dosis inicial y 4 horas después de las dosis repetidas para análisis farmacocinético (PK).

Los objetivos primarios fueron: exposición temprana (índice de absorción, $AUC_{0-30 \text{ mins}}$, tanto después de la dosificación inicial como después de la dosificación repetida), variación inter(entre)-sujeto (inter-CV%, después de la dosis inicial) y variación intra-sujeto (intra-CV%, después de la dosificación repetida). Los objetivos secundarios incluyeron $AUC_{0-60 \text{ mins}}$, concentración en plasma a los 30 mins ($C_{pl \ 30 \text{ mins}}$) y porcentaje de fármaco absorbido (PDA) a los 30 y 60 minutos (medido por medio de análisis de desconvolución, varianza medida solamente para la dosis inicial).

33

Resultados

AUC_{0-30 mins} tanto para la dosis inicial como para después de la dosificación repetida fueron significativamente más altas para la formulación que contiene paracetamol/carbonato de calcio versus la formulación de paracetamol estándar (dosis inicial: 0.98 versus 0.10 µg.h/ml [diferencia de medianas 0.77, 95% CI 0.53-1.01, p<0.0001]; dosificación repetida: 1.23 versus 0.15 µg.h/ml [diferencia de medianas 0.99, 95% CI 0.81-1.19, p<0.0001]).

Inter-CV% para este parámetro fue significativamente más bajo para la formulación que contiene paracetamol/carbonato de calcio versus la formulación de paracetamol estándar (84.4% versus 192%, p<0.0001).

De manera similar, hubo una diferencia significativa para intra-CV% para AUC_{0-30 mins} (60.6% versus 116%, p<0.0001). Reducciones similares en inter-CV% e intra-CV% fueron observadas para AUC_{0-60 mins} y C_{pl} 30 mins junto con inter-CV% para PDA_{30 mins} y PDA_{60 mins}.

Conclusiones

Estos datos muestran claramente que la absorción de paracetamol con la formulación que contiene paracetamol/carbonato de calcio es significativamente más rápida que la absorción con tabletas de formulación de paracetamol estándar. De manera importante, la absorción de paracetamol con la formulación que contiene paracetamol/carbonato de calcio muestra también una variabilidad inter- e intra-sujeto significativamente menor.

Tomados juntos, estos datos tienen claras implicaciones clínicas en términos de una población de pacientes que obtiene un alivio del dolor rápido y consistente con esta valiosa terapia para el dolor de primera línea y, por lo tanto, evita problemas de efectos secundarios potenciales con tratamientos de segunda línea tales como los NSAIDs.

EJEMPLO 3

Desintegración y vaciamiento gástrico

La desintegración y disolución de tabletas son factores clave en la velocidad de absorción *in vivo* y parámetros farmacocinéticos posteriores. Usando la formulación que contiene paracetamol/carbonato de calcio se realizó una investigación de gamma escintigrafía *in vivo* de desintegración de tabletas y vaciamiento gástrico (GE).

15

Métodos

Este estudio de una sola dosis, cruzado involucró 24 voluntarios sanos. Todos los participantes tomaron un desayuno radiomarcado estándar 2 horas (h) antes de tomar el medicamento de estudio (1 g de paracetamol ya sea como una formulación que contiene paracetamol/carbonato de calcio (antes descrita) o una formulación en tableta de paracetamol estándar antes descrita (SP) [tableta marcada con $^{111}\text{indio-DTPA}$]).

3A

El índice de desintegración se midió usando gamma escintigrafía después de definir el área del estómago como la región de interés. Los datos fueron analizados usando el programa de análisis de imagen WebLink®. El inicio y terminación de la desintegración de la tableta fueron determinados mediante evaluación cualitativa de imágenes escintigráficas. El vaciamiento gástrico de la tableta fue determinado mediante cuantificación de la cantidad de actividad que quedaba en el estómago en una serie de puntos de tiempo. Se usaron dos parámetros para evaluar GE: tiempo hasta 50% de vaciamiento (T_{50}) y tiempo hasta 90% de vaciamiento (T_{90}). El inicio de GE se determinó mediante evaluación cualitativa de imágenes escintigráficas.

Resultados

Tanto el tiempo hasta el inicio como el tiempo hasta la terminación de la desintegración fueron significativamente más rápidos para la formulación que contiene paracetamol/carbonato de calcio que para la formulación de paracetamol estándar (6.4 ± 4.3 versus 46.7 ± 20.5 min, $p < 0.0001$ y 12.9 ± 26.4 versus 69.6 ± 30.2 min, $p < 0.0001$). De manera similar, para GE, el tiempo hasta el inicio (41.9 ± 28.8 versus 85.0 ± 28.2 , $p < 0.0001$), T_{50} (72.4 ± 36.4 versus 100.7 ± 30.6 , $p = 0.0013$) y T_{90} (128.4 ± 41.2 versus 142 ± 33.8 , $p = 0.10$) fueron más cortos para la formulación que contiene paracetamol/carbonato de calcio que para la formulación de paracetamol estándar. El tiempo para GE de la comida estándar no difirió entre la formulación que contiene paracetamol/carbonato de calcio o la formulación de

paracetamol estándar. Además, aunque 75% de los sujetos que tomaron la formulación que contiene paracetamol/carbonato de calcio mostró inicio de desintegración/disolución en 5 minutos, ninguno del grupo estándar mostró inicio en este punto de tiempo.

5

Conclusiones

La formulación que contiene paracetamol/carbonato de calcio tuvo una ventaja de desintegración de tableta *in vivo* altamente significativa con respecto a la formulación de paracetamol estándar en este estudio de escintigrafía. Esto se correlaciona con un GE mejorado para paracetamol con la formulación que contiene paracetamol/carbonato de calcio en comparación con formulaciones de paracetamol estándar.

Todas las publicaciones, incluyendo mas no limitadas a patentes y solicitudes de patente, citadas en esta especificación se incorporan en la presente como referencia como si se indicara específica e individualmente que cada publicación individual se incorpora como referencia en la presente tal como quedamente completamente establecido.

La descripción anterior describe completamente la invención incluyendo modalidades preferidas de la misma. Modificaciones y mejoras de las modalidades específicamente descritas en la presente se encuentran dentro del alcance de las siguientes reivindicaciones. Sin más explicación en detalle, se cree que el experto en la técnica puede, usando la descripción anterior, utilizar la presente invención al máximo. Por lo tanto, los ejemplos en

20



la presente se deben interpretar como meramente ilustrativos y no una limitación del alcance de la presente invención en modo alguno. Las modalidades de la invención en las cuales se reclama una propiedad o privilegio exclusivo se definen como sigue.

NOVEDAD DE LA INVENCION

REIVINDICACIONES

- 5 1.- Un método para reducir la variabilidad intrapaciente en formulaciones que contienen paracetamol en pacientes que tienen dismotilidad gástrica que comprende administrar a dicho paciente que lo necesita, una forma de dosificación farmacéutica administrada oralmente que comprende un primer agente activo, carbonato de calcio, al menos un primer
- 10 agente aglutinante, y al menos un agente desintegrante como componentes intragranulares en forma de un material granulado, y como un componente extragranular al menos un coloide hidrofílico, de manera opcional un segundo agente aglutinante, carbonato de calcio, un superdesintegrante y un segundo agente activo.
- 15 2.- El método de conformidad con la reivindicación 1, caracterizado además porque el paciente es un paciente diabético.
- 3.- El método de conformidad con las reivindicaciones 1 o 2, caracterizado además porque el primer agente activo es paracetamol y porque el agente extragranular opcional comprende un segundo agente aglutinante
- 20 presente en una cantidad que varía de aproximadamente 0.1% a aproximadamente 10.0% en peso de la cantidad de agente aglutinante intragranular en el mismo.

4.- El método de conformidad con las reivindicaciones 1 a 3, caracterizado además porque el componente extragranular opcional comprende una segunda cantidad de carbonato de calcio presente en una cantidad que varía de aproximadamente 0.1% a aproximadamente 10.0% en peso de la cantidad de carbonato de calcio intragranular en el mismo.

5.- El método de conformidad con las reivindicaciones 1 a 4, caracterizado además porque el componente extragranular opcional comprende un segundo principio activo que es paracetamol presente en una cantidad que varía de aproximadamente 0.1% a aproximadamente 10.0% en peso de un primer agente activo intragranular que es paracetamol.

6.- El método de conformidad con las reivindicaciones 1 a 4, caracterizado además porque el componente extragranular opcional comprende un superdesintegrante presente en una cantidad que varía de aproximadamente 0.1% a aproximadamente 5.0% en peso de la composición.

7.- El método de conformidad con las reivindicaciones 1 a 6, caracterizado además porque el coloide hidrofílico se selecciona de ácido algínico, carragenina, gelatina, pectina, agar o una combinación de dos o más de los mismos.

8.- El método de conformidad con la reivindicación 7, caracterizado además porque el coloide hidrofílico comprende ácido algínico.

9.- El método de conformidad con cualquiera de las reivindicaciones 1 a 8, caracterizado además porque el coloide hidrofílico está

presente en una cantidad que varía de aproximadamente 1.0% a aproximadamente 5.0% en peso de la composición.

10.- El método de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque la forma de dosificación
5 adicionalmente comprende como un componente extragranular un colorante, tinte, saborizante, edulcorante, lubricante o agente resbalador, o una combinación de dos o más de los mismos.

11.- El método de conformidad con la reivindicación 1, caracterizado además porque la forma de dosificación es una tableta ingerible
10 que comprende paracetamol, carbonato de calcio, almidón pregelatinizado, y cualesquier otros componentes intragranulares opcionales combinados juntos en un procedimiento de granulación para formar un material granulado, y luego mezclados con ácido algínico y cualesquier otros componentes
extragranulares opcionales para formar una mezcla, y después comprimidos
15 para formar una tableta.

12.- El método de conformidad con la reivindicación 1, caracterizado además porque la forma de dosificación es una tableta ingerible que comprende un material granulado que contiene como componentes intragranulares paracetamol, carbonato de calcio, y al menos un agente
20 aglutinante que es celulosa microcristalina o almidón, y en donde el almidón se selecciona el grupo que consiste de almidón de maíz, almidón de maíz modificado, almidón de trigo, almidón de trigo modificado, almidón de papa, almidón pregelatinizado o una combinación de dos o más almidones de los

37

mismos, con la condición de que si el agente aglutinante comprende una mezcla de almidón de maíz y almidón pregelatinizado entonces la relación en peso de almidón pregelatinizado a almidón de maíz es mayor que de aproximadamente 3.0 a 1.0; y de manera opcional un agente desintegrante
5 combinado junto en un procedimiento de granulación para formar un material granulado; y que contiene como componentes extragranulares un coloide hidrofílico seleccionado de ácido algínico, carragenina, gelana, pectina, agar o una combinación de dos o más de los mismos; y de manera opcional al menos un excipiente extragranular que es un segundo agente activo, una
10 segunda cantidad de carbonato de calcio, un segundo agente desintegrante, un segundo agente aglutinante, un colorante, tinte, saborizante, edulcorante, lubricante, o agente resbalador, o una combinación de dos o más de los mismos, y los componentes son comprimidos en una tableta.

13.- El método de conformidad con la reivindicación 12,
15 caracterizado además porque el coloide hidrofílico es ácido algínico.

14.- El método de conformidad con las reivindicaciones 12 o 13, caracterizado además porque el coloide hidrofílico está presente en una cantidad que varía de aproximadamente 1.0% a aproximadamente 5.0% en peso de la composición.

20 15.- El método de conformidad con la reivindicación 12, caracterizado además porque el material granulado comprende un agente desintegrante que es un superdesintegrante presente en una cantidad que

varía de aproximadamente 0.5% a aproximadamente 5.0% en peso de la composición.

16.- El método de conformidad con la reivindicación 12, caracterizado además porque el agente aglutinante intragranular es un almidón pregelatinizado.

17.- El método de conformidad con la reivindicación 16, caracterizado además porque el almidón está presente en una cantidad que varía de aproximadamente 5.0% a aproximadamente 20.0% en peso de la composición.

18.- El método de conformidad con la reivindicación 12, caracterizado además porque el agente aglutinante comprende un primer agente aglutinante y un segundo agente aglutinante, y en donde el primer agente aglutinante es almidón.

19.- El método de conformidad con la reivindicación 18, caracterizado además porque el segundo agente aglutinante es PVP.

20.- El método de conformidad con cualquiera de las reivindicaciones 1 a 19, caracterizado además porque el agente activo intragranular es paracetamol, y está presente en una cantidad que varía de aproximadamente 60.0% a aproximadamente 80.0% en peso de la composición.

21.- El método de conformidad con cualquiera de las reivindicaciones 1 a 20, caracterizado además porque el carbonato de calcio

30

intragranular está presente en una cantidad que varía de aproximadamente 5.0% a aproximadamente 20.0% en peso de la composición.

22.- El método de conformidad con cualquiera de las reivindicaciones 1 a 20, caracterizado además porque el contenido de
5 carbonato de calcio intragranular en el material granulado no excede de 20.0% en peso de la composición.

23.- Un método para mejorar la analgesia en un paciente diabético que comprende administrar a dicho paciente que lo necesita, una forma de dosificación farmacéutica administrada oralmente que comprende un
10 primer agente activo, carbonato de calcio, al menos un primer agente aglutinante, y al menos un agente desintegrante como componentes intragranulares en la forma de un material granulado, y como un componente extragranular al menos un coloide hidrofílico, de manera opcional un segundo agente aglutinante, carbonato de calcio, un superdesintegrante, y un segundo
15 agente activo.

24.- Un método para mejorar la absorción de paracetamol en un paciente con dismotilidad gástrica que comprende administrar a dicho paciente que lo necesita, una forma de dosificación farmacéutica administrada oralmente que comprende un primer agente activo, carbonato de calcio, al
20 menos un primer agente aglutinante, y al menos un agente desintegrante como componentes intragranulares en forma de un material granulado, y como un componente extragranular al menos un coloide hidrofílico, de manera

opcional un segundo agente aglutinante, carbonato de calcio, un superdesintegrante, y un segundo agente activo.

- 25.- Un método para mejorar la analgesia en un paciente diabético que comprende administrar a dicho paciente que lo necesita, una
- 5 forma de dosificación farmacéutica administrada oralmente que comprende: a) paracetamol; b) al menos un agente que contribuye a la disolución seleccionado de carbonato de sodio, carbonato de amonio, bicarbonato de sodio, bicarbonato de potasio, carbonato de calcio, carbonato de magnesio, carbonato de glicina disódico, carbonato de glicina sódico, carbonato de lisina,
- 10 arginina, o combinaciones de dos o más de los anteriores; c) al menos un agente de absorción de agua seleccionado de polivinilpirrolidona entrelazada (crospovidona), croscarmelosa de sodio, glicolato de almidón de sodio, povidona, almidón, derivados de almidón, hidroxipropilcelulosa de baja sustitución, hidroxipropilcelulosa, ácido algínico, alginato de sodio, sulfato de
- 15 calcio, carboximetilcelulosa de calcio, celulosa microcristalina, celulosa en polvo, dióxido de silicio coloidal, docusato sódico, goma guar, silicato de magnesio aluminio, metilcelulosa, polacrilina potásica, celulosa microcristalina silicificada, óxido de magnesio, tragacanto, manitol, sorbitol, xilitol, sacarosa, lactosa, fructosa, maltosa, polietilenglicol, aminoácidos, ciclodextrina, urea y/o
- 20 polivinilpirrolidona; y en donde al menos 70 del paracetamol es disuelto a partir de la formulación a los 180 segundos en un aparato de disolución USP 2 con 900 ml de ácido clorhídrico 0.05 N a 30 rpm y 37°C.

RESUMEN DE LA INVENCIÓN

La presente invención está dirigida a un método novedoso para reducir la variabilidad intrapaciente en un agente farmacéuticamente activo

5 que de manera adecuada no es absorbido en el estómago, tal como formulaciones que contienen paracetamol en pacientes que tienen dismotilidad gástrica, o un método para mejorar la analgesia en un paciente diabético, o mejorar la absorción de un agente activo en un paciente con dismotilidad gástrica, dichos métodos comprenden administrar oralmente a

10 dicho paciente que lo necesita una forma de dosificación farmacéutica que comprende un primer agente activo, carbonato de calcio, al menos un primer agente aglutinante, y al menos un agente desintegrante como componentes intragranulares en forma de un material granulado, y como un componente extragranular al menos un coloide hidrofílico, de manera opcional un segundo

15 agente aglutinante, carbonato de calcio, un superdesintegrante, y un segundo agente activo.

20

37B

P11/76F

File Copy
PATENT COOPERATION TREATY

PCT/US2009/052039

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

DINNER, Dara, L.
c/o Glaxosmithkline
Corporate Intellectual Property, UW2220
709 Swedeland Road, P.o. Box 1539
King Of Prussia, PA 19406-0939
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
05 February 2010 (05.02.2010)

Applicant's or agent's file reference
CU63096

IMPORTANT NOTIFICATION

International application No.
PCT/US2009/052039

International filing date (day/month/year)
29 July 2009 (29.07.2009)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address

SMITHKLINE BEECHAM CORPORATION
One Franklin Plaza
P.o. Box 7929
Philadelphia, PA 19101
United States of America

State of Nationality
US

State of Residence
US

Telephone No.
610-270-5017

Facsimile No.
610-270-5090

E-mail address
US_CIPKOP@GSK.COM

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

GLAXOSMITHKLINE LLC
One Franklin Plaza
200 North 16th Street
Philadelphia, PA 19102
United States of America

State of Nationality
US

State of Residence
US

Telephone No.
610-270-5017

Facsimile No.
610-270-5090

E-mail address
us_cipkop@gsk.com
☒ Notifications by e-mail authorized

3. Further observations, if necessary:

The request for recording of the above change was received by the International Bureau between 20 and 30 months from the priority date.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search

☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Laniel David

e-mail pt04.pct@wipo.int

Telephone No. +41 22 338 74 04

Facsimile No. +41 22 338 89 95

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

DARA L. DINNER
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY,
UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

22 SEP 2009

Applicant's or agent's file reference
CU63096

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.
PCT/US 09/52039

International filing date
(day/month/year) 29 July 2009 (29.07.2009)

Applicant SMITHKLINE BEECHAM CORPORATION

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference CU63096	FOR FURTHER ACTION		see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 09/52039	International filing date (day/month/year) 29 July 2009 (29.07.2009)	(Earliest) Priority Date (day/month/year) 30 July 2008 (30.07.2008)	
Applicant SMITHKLINE BEECHAM CORPORATION			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (see Box No. II).

3. ☐ Unity of invention is lacking (see Box No. III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/52039

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-10 and 20-22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/52039

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 37/18, A61K 31/16 (2009.01)

USPC - 514/629

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC -- 514/629Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-- 424/400, 424/465, 424/692 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST -- PGPB,USPT,USOC,EPAB,JPAB; Dialog Classic Files ? 654, 652, 351, 349, 315, 6, 35, 65, 155; Google Scholar; USPTO Web Page; Search terms -- standardized dose, paracetamol, povidone, crospovidone, gastric dysmotility, diabetes, alginate acid, pregelatinized starch, binding agents, calcium carbonate, dissolution test

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/0141144 A1 (ROBERTS et al.) 02 June 2007 (02.06.2007) para [0002], [0018], [0031], [0050], [0057], [0073], [0078], [0087]-[0088], [0101], [0138]-[0139], [0210],	1-3, 11-19, 23-25
Y	US 2004/0126318 A1 (EPHREPREIS) 01 July 2004 (01.07.2004) para [0003], [0017]-[0019], [0035]-[0036], [0038]-[0039], [0065], [0078], [0085]-[0086]	1-3, 11-19, 23-25
Y	US 2004/0170681 A1 (GRATTAN) 02 September 2004 (02.09.2004) para [0001], [0011], [0016], [0021], [0035], [0037]	3, 11-19

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 2009 (10.09.2009)

Date of mailing of the international search report

22 SEP 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: DARA L. DINNER
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY,
UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

22 SEP 2009

Applicant's or agent's file reference
CU63096

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 09/52039

International filing date (day/month/year)

29 July 2009 (29.07.2009)

Priority date (day/month/year)

30 July 2008 (30.07.2008)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 37/18, A61K 31/16 (2009.01)

USPC - 514/629

Applicant SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion

11 September 2009 (11.09.2009)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US 09/52039

26

Box No. 1 Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/52039

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-10 and 20-22

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 4-10 and 20-22 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-10 and 20-22 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 4-10 and 20-22

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 09/52039

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-3, 11-19, 23-25	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-3, 11-19, 23-5	NO
Industrial applicability (IA)	Claims	1-3, 11-19, 23-25	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-2 and 23-25 lack an inventive step under PCT Article 33(3) as being obvious over US 2007/0141144 A1 to Roberts et al. (hereinafter 'Roberts') in view of US 2004/0126318 A1 to Ephrenpreis.

Regarding claim 1, Roberts teaches a method for reducing inpatient variability in paracetamol containing formulations (para [0073], meeting dissolution standard for formulations of paracetamol) comprising an orally administered (para [0002]) pharmaceutical dosage form (para [0031], tablet) comprising a first active agent (para [0002], oral paracetamol), calcium carbonate (para [0057], [0098]), at least one first binding agent (para [0050]), and at least one disintegrating agent (para [0086]) as intragranular components (para 0210), mixed for granulation) in the form of a granulate (para [0081]), and as an extragranular component at least one hydrophilic colloid (para [0087], alginic acid). Roberts does not specifically teach that the formulations of paracetamol are for administration to patients in need thereof having gastric dysmotility. Ephrenpreis teaches treating (para [0017]) gastric dysmotility (para [0003], [0035], [0039], gastroparesis) in patients need thereof (para [0035], [0036], [0039], patients with diabetic gastroparesis) with paracetamol (para [0019], acetaminophen). Ephrenpreis also teaches monitoring gastric emptying (para [0003], [0018]) with various formulations of paracetamol (acetaminophen) (para [0003], [0018]). It would have been obvious to one of skill in the art to combine the teachings of Roberts and Ephrenpreis to reduce inpatient variability in paracetamol containing formulations by administering paracetamol in the formulation described above to patients exhibiting gastric dysmotility, because the monitoring of paracetamol formulations for their effect on gastric emptying in patients with gastric dysmotility as taught by Ephrenpreis would have been expected to allow a determination to be made of the efficacy of a paracetamol formulation as taught by Roberts in individuals with the condition.

Regarding claim 2, further to the method according to Claim 1, as described above, Ephrenpreis teaches that the patient is a diabetic patient (para [0035], [0039]).

Regarding claim 23, Roberts teaches analgesia (para [0002], pain relief) from an orally administered (para [0002]) pharmaceutical dosage form (para [0031], tablet) comprising a first active agent (para [0002], oral paracetamol), calcium carbonate (para [0057], [0098]), at least one first binding agent (para [0050]), and at least one disintegrating agent (para [0086]) as intragranular components (para 0210), mixed for granulation) in the form of a granulate (para [0081]), and as an extragranular component at least one hydrophilic colloid (para [0087], alginic acid). Roberts does not specifically teach that the formulation provides a method for improving analgesia in a diabetic patient comprising administering (the formulation) to said patient in need thereof. Ephrenpreis teaches treating (para [0017]) patients need thereof (para [0035], [0036], [0039], patients with diabetic gastroparesis) with the analgesic, paracetamol (para [0019], acetaminophen). Ephrenpreis also teaches monitoring gastric emptying (para [0003], [0018]) with various formulations of paracetamol (acetaminophen) (para [0003], [0018]) to determine the absorption characteristics of paracetamol (para [0085], [0086]). It would have been obvious to one of skill in the art to combine the teachings of Roberts and Ephrenpreis to provide a method for improving analgesia in a diabetic patient comprising administering a formulation of paracetamol, because improvement in analgesia from paracetamol would have been expected to be a function of its ability to be absorbed into the bloodstream in patients with gastroparesis as taught by Ephrenpreis when provided with a paracetamol formulation for enhanced absorption as taught by Roberts.

Regarding claim 24, Roberts teaches an orally administered (para [0002]) pharmaceutical dosage form (para [0031], tablet) comprising a first active agent (para [0002], oral paracetamol), calcium carbonate (para [0057], [0098]), at least one first binding agent (para [0050]), and at least one disintegrating agent (para [0086]) as intragranular components (para 0210), mixed for granulation) in the form of a granulate (para [0081]), and as an extragranular component at least one hydrophilic colloid (para [0087], alginic acid). Roberts does not specifically teach that the formulation provides a method for improving absorption of paracetamol in a patient with gastric dysmotility. Ephrenpreis teaches treating (para [0017]) gastric dysmotility (para [0003], [0035], [0039], gastroparesis) in patients need thereof (para [0035], [0036], [0039], patients with diabetic gastroparesis) with paracetamol (para [0019], acetaminophen). Ephrenpreis also teaches monitoring gastric emptying (para [0003], [0018]) with various formulations of paracetamol (acetaminophen) (para [0003], [0018]) to determine the absorption characteristics of paracetamol (para [0085], [0086]). It would have been obvious to one of skill in the art to combine the teachings of Roberts and Ephrenpreis to administer to a patient in need thereof, an orally administered pharmaceutical dosage form comprising paracetamol in the formulation described above, because improvement in absorption of paracetamol as monitored by Ephrenpreis in patients with gastroparesis would have been expected when provided with a paracetamol formulation for enhanced absorption as taught by Roberts.

-----continued in Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 09/52039

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V 2. Citations and explanations:

Regarding claim 25, Roberts teaches an orally administered (para [0002]) pharmaceutical dosage form (para [0031], tablet) comprising:
a) paracetamol (para [0002]);
b) at least one agent which contributes to dissolution (para [0098], improved dissolution from pH modulation) which is calcium carbonate (para [0057], [0098]);
c) at least one water uptake agent (para [0087]) which is cross-linked polyvinylpyrrolidone (crospovidone) (para [0087]) wherein at least 70 of the paracetamol is dissolved from the formulation within 180 seconds in USP dissolution apparatus 2 with 900ml of 0.05 N hydrochloric acid at 30 rpm and 37°C (para [0067], [0073], [0084]). Roberts does not specifically teach a method for improving analgesia in a diabetic patient comprising administering to said patient in need thereof, an orally administered formulation as described above. Ephrenpreis as above teaches treating (para [0017]) patients need thereof (para [0035]-[0036], [0039], patients with diabetic gastroparesis) with the analgesic, paracetamol (para [0019], acetaminophen). Ephrenpreis also teaches monitoring gastric emptying (para [0003], [0018]) with various formulations of paracetamol (acetaminophen) (para [0003], [0018]) to determine the absorption characteristics of paracetamol (para [0085]-[0086]). It would have been obvious to one of skill in the art to combine the teachings of Roberts and Ephrenpreis to provide a method for improving analgesia in a diabetic patient comprising administering a formulation of paracetamol, because improvement in analgesia from paracetamol would have been expected to be a function of its ability to be absorbed into the bloodstream in patients with gastroparesis as taught by Ephrenpreis when provided with a paracetamol formulation which provides dissolution properties for enhanced absorption as taught by Roberts.

Claims 3 and 11-19 lack an inventive step under PCT Article 33(3) as being obvious over Roberts in view of Ephrenpreis and further in view of US 2004/0170681 A1 to Grattan.

Regarding claim 3, further to the method according to Claim 1, as described above, Roberts teaches that the first active agent is paracetamol (para [0002]), and also teaches an optional extragranular agent which comprises a second binding agent present (para [0087], polyvinylpyrrolidone), but neither Roberts nor Ephrenpreis specifically teaches that the second binding agent is present in an amount ranging from about 0.1% to about 10.0% by weight of the intragranular binding agent amount therein. Grattan teaches a swallow tablet formulation of paracetamol (para [0001]) which comprises a first binding agent (para [0021], [0037], pregelatinized starch) and a second binding agent (para [0021], [0037], polyvinylpyrrolidone) wherein the ratio of the second to the first agents is about 0.1% to about 10.0% by weight of the intragranular binding agent (para [0021], [0037], 50:2, starch to povidone). It would have been obvious to one of skill in the art to combine the teachings of Roberts, Ephrenpreis and Grattan to provide two binding agents, one granular (pre-gelatinized starch) the other extragranular (PVP) in a ratio of about 0.1% to about 10.0% by weight for the extragranular to the intragranular binding agent, because of the teaching of a paracetamol formulation comprising both binding agents in an appropriate ratio.

Regarding claim 11, further to the method according to Claim 1, as described above, Roberts teaches that the dosage form is a swallow tablet (para [0031]) comprising paracetamol (para [0002]) and calcium carbonate (para [0057], [0098]), combined together in a granulation process (para [0210]) to form a granulate (para [0081]), and then admixed with alginic acid (para [0087]) to form a blend (para [0138], [0139], [0167]), and then compressed to form a tablet (para [0139]). Grattan as above teaches a swallow tablet formulation of paracetamol (para [0001]) which comprises pregelatinized starch (para [0021], [0037], pregelatinized starch). It would have been obvious to one of skill in the art to combine the teachings of Roberts, Ephrenpreis and Grattan to add pregelatinized starch to form the granular portion of the tablet prior to mixing with alginic acid in a blend for compression into a tablet, because the pregelatinized starch as taught by Grattan is used in paracetamol tablets and would have been expected to function as a binder for the granular portion of the blend.

Regarding claim 12, further to the method according to Claim 1, as described above, Roberts teaches that the dosage form is a swallow tablet (para [0031]) comprising a granulate (para [0081]) containing as intragranular components paracetamol (para [0002]), calcium carbonate (para [0057], [0098]), and at least one binding agent (para [0050]) which is microcrystalline cellulose (para [0087]), and also comprising a starch (para [0082]) and a hydrophilic colloid which is alginic acid (para [0087]). Neither Roberts nor Ephrenpreis specifically teaches that the starch is selected from the group consisting of corn (maize) starch, modified corn starch, wheat starch, modified wheat starch, potato starch, pregelatinized starch or a combination of two or more starches thereof. Grattan teaches a swallow tablet formulation of paracetamol (para [0001]) which comprises pregelatinized starch (para [0021], [0037], pregelatinized starch). It would have been obvious to one of skill in the art to combine the teachings of Roberts, Ephrenpreis and Grattan to form a tablet by compression wherein the starch is pregelatinized starch based on the teaching of this form of use in swallow tablets of paracetamol by Grattan.

Regarding claim 13, further to the method according to Claim 12, as described above, Roberts teaches that the hydrophilic colloid is alginic acid (para [0087]).

Regarding claim 14, further to the method according to Claim 12, as described above, Roberts teaches that the hydrophilic colloid (para [0087], alginic acid) is present in an amount ranging from about 1.0% to about 5.0% by weight of the composition (para [0087], [0088], 2-80% for the amount of water uptake agents, in which alginic acid is classified).

Regarding claim 15, further to the method according to Claim 12, as described above, Roberts teaches that the granulate (para [0081]) comprises a disintegrating agent (para [0086]) which is a super disintegrant (para [0087], crospovidone) present in an amount ranging from about 0.5% to about 5.0% by weight of the composition (para [0087], [0088], 2-80% for the amount of water uptake agents, in which crospovidone is classified).

Regarding claim 16, further to the method according to Claim 12, as described above, Grattan teaches that the intragranular binding agent (para [0016]) is a pregelatinized starch (para [0021], [0037]).

-----continued in next Supplemental Box-----

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational application No.
PCT/US 09/52039

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Prior Supplemental Box:

Regarding claim 17, further to the method according to Claim 16, as described above, Grattan teaches that the starch (para [0021], [0037], pregelatinized starch) is present in an amount ranging from about 5.0% to about 20.0% by weight of the composition (para [0035], 75 mg of 660-mg total composition).

Regarding claim 18, further to the method according to Claim 12, as described above, Roberts teaches that the binding agent (para [0050], binders) comprises a first binding agent and a second binding agent (para [0087], polyvinylpyrrolidone), and wherein the first binding agent is starch (para [0082]).

Regarding claim 19, further to the method according to Claim 18, as described above, Roberts teaches that the second binding agent is PVP (para [0087]).

Claims 1-3, 11-19 and 23-25 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.



Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
GLAXOSMITHKLINE LLC

REFERENCIA	Radicación No.	11 009937
	Solicitud internacional	PCT/US2009/052039
	Fecha inicio fase nacional	28/02/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	05721

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo título que permita identificar la materia de la cual trata la solicitud, ya que el título relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continúa en la página siguiente...



Continuación radicado No: 11 009937

52

Industria y Comercio
SUPERINTENDENCIA

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 31 MAR 2011.
adpa11



Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
GLAXOSMITHKLINE LLC

REFERENCIA	Radicación No.	11 009937
	Solicitud internacional	PCT/US2009/052039
	Fecha inicio fase nacional	28/02/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

05722

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (c)

31 MAR. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha _____
adpa11