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División de Nuevas Creaciones

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04-77244

54. TITULO NUEVA COMPOSICIÓN.

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A61K31/426

71. SOLICITANTE ELAXO GROUP LIMITED

DOMICILIO REINO UNIDO, GRAN BRETAÑA

74. APODERADO ALVARO CORREA OROÑEZ
T.P. 20.281

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

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SOLICITUD DE :

☒ X

Patente de Invención

☐

Patente de Modelo de Utilidad

☐

Capítulo I.

☒ X

Capítulo II.

②

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(71)

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IDENTIFICACION

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C.E.

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Otro

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Cual

Número

③

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IDENTIFICACION

C.C.

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Usaquén

TP 20.281

④

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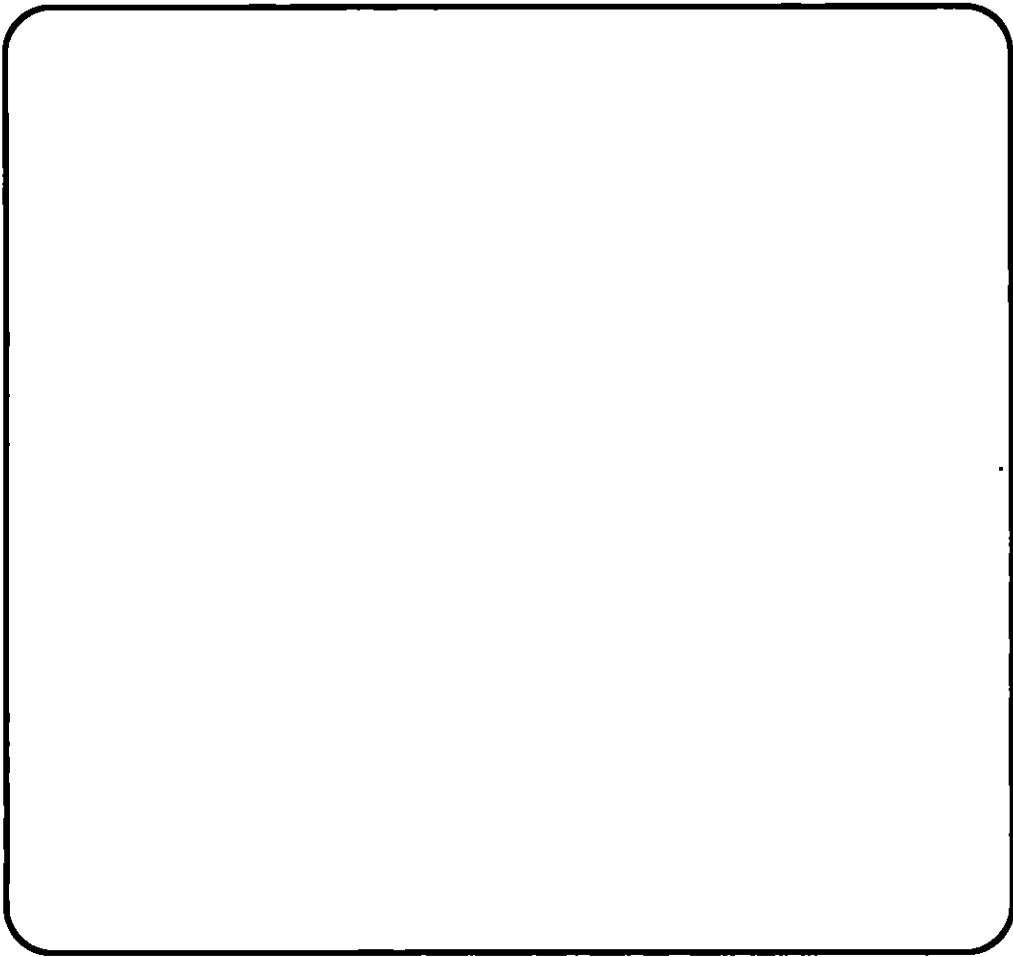
10

ANEXOS

- ☒ 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
- ☐ 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 acredita 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:

11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA: 

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Usaquén

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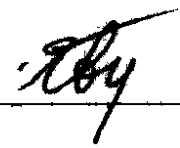
***** CONSIGNACION *****

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***** CONCEPTO *****

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
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- (74) Agent: GIDDINGS, Peter, John; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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(54) Title: ORAL DOSAGE FORM FOR CONTROLLED DRUG RELEASE

(57) Abstract: An oral dosage form comprising, (i) an erodible core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and (ii) an erodible coating surrounding said core, which coating comprises one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core; characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the dosage form occurs through the said opening(s) by the erosion of said erodible core and through erosion of said erodible coating under pre-determined pH conditions; a process for preparing such a dosage form and the use of such a dosage form in medicine.

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ORAL DOSAGE FORM FOR CONTROLLED DRUG RELEASE

Field of the invention

5 The invention relates to an oral dosage form which provides controlled release of an active pharmaceutical agent in different body environments, to a process for preparing such a dosage form and to the use of such a dosage form in medicine.

Background to the invention

10 The use of a coating to control the rate of release of an active agent has received considerable attention and many different devices have been developed for such a purpose. For example, International Patent Application, Publication Number WO 01/05430 describes a drug delivery device that enables the delivery of drug substances which exhibit pH dependent solubility, in particular compounds that are more soluble at low pH levels (less than pH 2) than at near neutral levels (greater than about pH 5). Such
15 delivery devices are characterised by the presence of a coating that is impermeable and insoluble in the fluid of the environment of use.

International patent application, Publication Number WO 95/30422 describes a series of controlled-release dosage forms of azithromycin. In particular, there is
20 described a series of dosage forms that reduce the exposure of the upper GI tract (e.g. the stomach) to high concentrations of azithromycin, by the use of a pH dependent coating. Such dosage forms do not feature openings through which release of the drug substance may occur.

25 US Patent Number 6,099,859 describes a controlled release tablet for the delivery of an antihyperglycemic drug, which comprises an osmotically active drug-containing core and a semipermeable membrane, wherein the semipermeable membrane is permeable to the passage of water and biological fluids and is impermeable to the passage of the drug substance. The semipermeable membrane contains at least one
30 passageway for the release of the antihyperglycemic drug.

Additional devices that utilise a coating to control the rate of release of an active agent are discussed in US Patent Number 5,004,614. This patent describes a tablet core provided with an outer coating that is substantially impermeable to environmental fluid.
35 The said outer coating may be prepared from materials that are either insoluble or soluble in the environmental fluids. Where a soluble material is used, the coating is of sufficient thickness that the core is not exposed to environmental fluid before the desired duration of the controlled release of the active agent has passed. Through this

impermeable outer coating, one or more opening(s) has been created, so as to provide environmental fluids with an access route to the core. Therefore, upon ingestion of the coated tablet, gastro-intestinal fluid can enter the opening(s) and contact or penetrate the core, to release the active agent. The result is that the active agent is released in a controlled manner out of the opening(s) only. The preferred geometry is such that there is a circular hole on the top and bottom face of the coated tablet. The opening(s) in question have an area from about 10 to 60 percent of the face area of the coated tablet. The rate of drug release is found to be directly related to the diameter of the opening(s) and to the solubility of the matrix core and active agent, allowing the possibility for a variety of drug release profiles be it zero or first order release.

This invention is based on the finding that the substantially impermeable coatings of US 5,004,614 are not suitable for the controlled release of all active agents, especially pharmaceutically active weak bases or pharmaceutically acceptable salts and solvates thereof. Such active agents exhibit a marked pH dependent solubility, i.e. they are more soluble at around pH 2, associated with regions found in the stomach, compared to their solubility in the generally neutral conditions of the small intestine, around pH 7.

We have found that for administration of a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, where it is desirable that release of the active compound takes place in more than one pH environment, it is beneficial for the coating to be erodable or soluble in a pH dependent manner.

Summary of the invention

Accordingly, in its broadest aspect the present invention provides an oral dosage form comprising an erodable core which contains a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, the core having a coating with one or more openings leading to the core, characterized in that the coating is erodable under predetermined pH conditions.

The present invention further provides an oral dosage form comprising,
(i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and
(ii) an erodable coating around said core, which coating comprises one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core;
characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the erodable core occurs

substantially through the said opening(s) and through erosion of said erodable coating under pre-determined pH conditions.

For the avoidance of doubt, as used herein the term "weak base" shall mean any
5 base the conjugate acid of which has a pKa of less than 11.5; in accordance with *The Pharmaceutical Handbook*, 19th Edition, 1980. The term "pharmaceutically acceptable weak base" shall be interpreted accordingly. Suitably, pharmaceutically acceptable weak bases or pharmaceutically acceptable salts or solvates thereof for use in the present invention exhibit a marked pH dependent solubility. Preferably, pharmaceutically
10 acceptable weak bases or pharmaceutically acceptable salts or solvates thereof for use in the present invention are more soluble in the pH range from 1 to 3 compared to their solubility in the pH range from 4.5 to 8. Preferred pharmaceutically acceptable weak bases or pharmaceutically acceptable salts or solvates thereof for use in the present invention are more soluble in the acidic conditions found in the mammalian stomach
15 than in the near neutral conditions of the mammalian intestines.

Suitable pharmaceutically active weak bases for use in the present invention include - 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone ("bupropion"), 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one
20 ("ondansetron"), (3S-*trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ("paroxetine"), α^1 -[[1,1-Dimethylethyl)amino]methyl]-4-hydroxy-1,3-benzenedimethanol ("salbutamol") and pharmaceutically acceptable salts and/or solvates thereof.

25 European Patent Application, Publication Number 0 306 228 A1 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0 306 228 A1 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound A'). International Patent Application, Publication Number WO
30 94/05659 discloses certain salts of Compound A including the maleate salt at Example 1 thereof.

Compound A and pharmaceutically acceptable salts or solvates thereof have useful pharmaceutical properties. In particular Compound A or a salt or solvate thereof
35 is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

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A preferred pharmaceutically active weak base for use in the present invention is Compound A or a pharmaceutically acceptable salt or solvate thereof. A particularly preferred pharmaceutically active weak base for use in the present invention is the maleate salt of Compound A.

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A further preferred pharmaceutically active weak base for use in the present invention is valaciclovir or a pharmaceutically acceptable salt thereof. Valaciclovir is the L-valine ester of acyclovir and is named 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl L-valinate. A preferred salt of this compound is the hydrochloride salt, known as valaciclovir hydrochloride. Valaciclovir and the hydrochloride salt thereof are disclosed in US Patent Number. 4,957,924 (see particularly Example IB), European Patent Number EP 0 308 065 B1 (see particularly Example IB), and L.M. Beauchamp et al, *Antiviral Chemistry and Chemotherapy*, 3(3), 157-164 (1992) (see particularly page 162 column 1), all of which are incorporated herein by reference as though fully set forth. A preferred anhydrous crystalline form of valaciclovir hydrochloride is disclosed in International Patent Application, Publication Number WO 96/22291 (incorporated herein by reference as though fully set forth); this anhydrous crystalline form can for example be defined by having substantially the X-ray powder diffraction pattern of one or more of Figures 1 to 3 of WO 96/22291. Some syntheses of valaciclovir and its hydrochloride salt are given in WO 96/22291, e.g. see Examples 1A/B and 2A/B and pages 4-7 therein.

Valaciclovir or a salt thereof can be used in the treatment and/or suppression of a viral infection in a mammal such as a human, particularly a viral infection caused by the herpes group of viruses, e.g. herpes zoster and/or herpes simplex virus types 1 or 2. The following dosage regimes, wherein the doses are calculated as the valaciclovir free base, are given for guidance:

- (a) treatment of episodes of herpes simplex virus types 1 and 2 infection:- total daily dose of about 1 or 2 g administered at 500 mg twice a day or 1 g twice a day for 5 to 10 days;
- (b) suppression of recurrences of herpes simplex virus types 1 and 2 infections (e.g. genital herpes):- total daily dose about 250 to 1 g (e.g. 500 mg twice a day) for about one month to ten years, depending on the patient. As disclosed in WO 97/25989 (incorporated herein by reference), valaciclovir or a salt thereof can also be used in the suppression of recurrent genital herpes in a human at a once daily dose of from about 200 mg to about 1000 mg (e.g. 250 mg, 500 mg or 1000 mg) valaciclovir or a salt thereof (calculated as the free base) for an effective treatment period e.g. for ca. 2 months up to ca. 10 years.

(c) treatment of varicella zoster virus infections (herpes zoster, e.g. shingles):- total daily dose about 3 g administered at 1 g three times a day for 7 days;

(d) suppression of cytomegalovirus infections:- total daily dose about 8 g administered at 2 g 4 times a day; for transplant patients this daily dose is administered for three to six months for the period at risk; and for HIV positive patients a daily dose is administered as usually indicated for improving quality of life, for example for two years or more.

Suitably, the pharmaceutically acceptable weak base is selected from the group consisting of 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone ("bupropion"), 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one ("ondansetron") and (3S-*trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ("paroxetine"), 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl L-valinate ("valaciclovir"), Compound A and pharmaceutically acceptable salts and/or solvates thereof (hereafter "the Primary Compounds of the invention"). Suitably, the pharmaceutically acceptable weak base is 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone ("bupropion") or a pharmaceutically acceptable salt or solvate thereof. Suitably, the pharmaceutically acceptable weak base is 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one ("ondansetron") or a pharmaceutically acceptable salt or solvate thereof. Suitably, the pharmaceutically acceptable weak base is (3S-*trans*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine ("paroxetine") or a pharmaceutically acceptable salt or solvate thereof. More suitably, the pharmaceutically acceptable weak base is 2-[(2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl)methoxy]ethyl L-valinate ("valaciclovir"). Most suitably, the pharmaceutically acceptable weak base is Compound A or a pharmaceutically acceptable salt or solvate thereof.

Brief description of the drawings

Figure 1 is a graph of dissolution against time for two formulations of oral dosage form in accordance with this invention.

Detailed description of the invention

Typical pharmaceutically active weak bases for use in the present invention are the Primary Compounds of the invention, in particular Compound A or a pharmaceutically acceptable salt or solvate thereof. Such compounds and pharmaceutically acceptable salts thereof exhibit a marked pH dependent solubility, i.e. they are more soluble at around pH 2, associated with regions found in the stomach,

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compared to their solubility in the generally neutral conditions of the small intestine, around pH 7.

5 The Primary Compounds of the invention and pharmaceutically acceptable salts and solvates thereof have useful pharmaceutical properties which are well documented (e.g. the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press)).

10 The oral dosage form of this invention may be also be used to administer other pharmaceutically active weak bases with similar dissolution properties to the Primary Compounds of the invention, to treat disorders for which the weak base is known to be indicated.

15 The above reference to the coating being erodable includes the situation where the coating disintegrates partially or wholly, or dissolves, or becomes porous, on contact with an environmental fluid so as to allow the fluid to contact the core. Suitably the coating disintegrates partially. Suitably the coating disintegrates wholly. Suitably the coating dissolves. Suitably the coating becomes porous.

20 Similarly the references to the core being erodable includes the situation where core disintegrates partially or wholly, or dissolves, or becomes porous, on contact with an environmental fluid so as to allow the fluid to contact the active agent. Suitably the core disintegrates partially. Suitably the core disintegrates wholly. Suitably the core dissolves. Suitably the core becomes porous.

25 While this invention provides that erosion of the coating is pH-dependent, the core may release the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof by eroding in a non-pH dependent manner. However to suit a
30 specific demand, the core may be a material which allows pH dependent erosion or disintegration of the core to release the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from its matrix.

35 Most suitably, although the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof is more soluble in the stomach than the intestines, the core is formulated so as to be erodable to substantially the same extent under both conditions.

So that the opening(s) in the coating retains its integrity and control of release rate, it is desirable that the pH dependent erosion of the coating has a defined threshold, i.e. the coating does not substantially erode except in the intestines. Thus, it is envisaged that erosion of the coating has a defined, pre-determined pH threshold at which it dissolves. Preferably, the coating erodes at pH > 4.5. More preferably, the coating erodes in the pH range from 4.5 to 8. Most preferably, the coating erodes in the pH range 5 to 7.

The present invention finds particular use in the situation where the coating erodes in the pH conditions of the intestines. Accordingly, the present invention also provides an oral dosage form comprising an erodable core which contains a pharmaceutically active weak base or a pharmaceutically acceptable salt thereof, the core having a coating with one or more openings leading to the core, characterised in that the coating is erodable under the pH conditions prevailing in a mammalian intestine.

It will be appreciated that the use of a coating that erodes at pH > 4.5 will restrict the amount of drug released into the acidic conditions associated with the stomach, since release is at low pH levels is substantially limited to diffusion of the active agent through the opening(s) in the erodable coating. Thus, the present invention is indicated to address the problem of "dose dumping" in the stomach for compounds that are more soluble in the pH range from 1 to 3 than in the pH range from 4.5 to 8. As the dosage form leaves a low pH environment and then encounters a higher environmental pH, e.g. moves from the stomach into the intestine, the coating will start to dissolve and erode away to expose all of the tablet core. During coat erosion, the available surface area to release drug is increased. The decrease in drug solubility and therefore rate of drug adsorption in the intestine can be compensated for by the increase in the surface area due to all the faces of the tablet core being exposed to erosion. The result is a more balanced drug release profile in both environments.

In applying the concepts of this invention, the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof may be incorporated into a conventional oral tablet or controlled release matrix (including both swellable and non-swellable systems). The matrix is formed into cores which are then coated with a material with pH-dependent erodability, for example a coating soluble at pH > 4.5, such as a polymethacrylate copolymer. One or more openings may then be drilled through the coatings using conventional techniques as disclosed in US 5,004,614.

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According to a further aspect of the present invention, there is provided a process for the preparation of an oral dosage form according to the present invention, which process comprises:

- (a) preparing an erodable tablet core;
- 5 (b) coating the core with a material with pH-dependent erodability; and
- (c) creating one or more openings in the coating, said opening(s) extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core.

10 The core may be prepared by compressing suitable ingredients to form a compacted mass which comprises the core of the dosage form (also referred to herein as "tablet core"). This may be prepared using conventional tablet excipients and formulation compression methods. Thus, the core typically comprises the active agent or agents along with excipients that impart satisfactory processing and compression
15 characteristics such as diluents, binders and lubricants. Additional excipients that may form part of the core of the device include disintegrants, flavourants, colorants, release modifying agents and/or solubilising agents such as surfactants, pH modifiers and complexation vehicles.

20 Suitable materials for the core include erodable polymethylmethacrylate resins such as the Eudragit™ series, for example Eudragit™ L30D, saccharoses, for example lactose and maltose, and cellulose esters, for example methylcellulose, hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose. Suitably, the core is predominantly hydroxypropylmethylcellulose and lactose. More suitably, the core
25 consists essentially of hydroxypropylmethylcellulose, lactose, colloidal silicon dioxide and magnesium stearate.

Typically the active agent and excipients are thoroughly mixed prior to compression into a solid core. The core of the device may be formed by wet granulation
30 methods, dry granulation methods or by direct compression. The core may be produced according to any desired pre-selected shape such as bi-convex, hemi-spherical, near hemi-spherical, round, oval, generally ellipsoidal, oblong, generally cylindrical or polyhedral, e.g. a triangular prism shape. The term "near hemi-spherical" is intended to be construed in the manner described in US 5,004,614. Suitably the core is formulated
35 into a bi-convex shape, e.g. having two domed opposite surfaces. In addition, the core may be produced in a multi-layered (e.g. bi- or tri- layered) form.

The quantity of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof present within the core is a matter to be determined based upon typical pharmaceutical considerations, e.g. known dosages for the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof, and is not limited by the process of this invention.

In particular, where Compound A or a pharmaceutically salt or solvate thereof is used in accordance with the present invention, a suitable dosage range is 2 to 12 mg. Thus, suitable dosage forms comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 2 to 4 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 4 to 8 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Particular dosage forms comprise 8 to 12 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

One dosage form comprises 2 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Preferred dosage forms comprise 4 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

Preferred dosage forms comprise 8 mg of Compound A or a pharmaceutically acceptable salt or solvate thereof.

The core may be coated with a suitable pH dependent erodable material by any pharmaceutically acceptable coating method. Examples include coating methods disclosed in US 5,004,614 and film coating, sugar coating, spray coating, dip coating, compression coating, electrostatic coating. Typical methods include spraying the coating onto the tablet core in a rotating pan coater or in a fluidised bed coater until the desired coating thickness is achieved. Suitably the coating is provided to add about 4 to 8 mg/cm² or 5 - 7 mg/cm² of dry polymer around the tablet surface area. Typically this results in an increase in weight (relative to the core) of from 3 - 10% or 5 - 10 % by weight. Suitably, the coating has a thickness in the range 0.05 to 0.5 mm.

Materials and their blends suitable for use as a pH-dependent erodable coating material in this invention include various polymethacrylate polymers, coprocessed polyvinylacetate phthalate, cellulose acetate trimellitate, cellulose acetate phthalate, shellac, hydroxypropylmethylcellulose phthalate polymers and their copolymers.

The coating material is suitably selected so that it is insoluble in stomach acid i.e. at pH 1.5 – 2, and is soluble or erodable in the small intestine i.e. at around pH 5.5 or in the large intestine i.e. at around pH 7. To achieve this, typically the material of the coating is erodable at pH of 4.5 or above.

5

Suitably, the coating material is selected from:

- cellulose acetate trimellitate (CAT) dissolving @ pH 4.8,
- polyvinyl acetate phthalate dissolving @ pH 5.0,
- hydroxypropylmethylcellulose phthalate 50 dissolving @ pH 5.2,
- 10 hydroxypropylmethylcellulose phthalate 55 dissolving @ pH 5.4,
- Acryl-eze™ dissolving @ pH 5.5,
- Aquateric™ dissolving @ pH 5.8,
- cellulose acetate phthalate dissolving @ pH 6.0,
- Eudragit™ L30 D dissolving @ pH 5.5,
- 15 Eudragit™ L dissolving @ pH 6.0,
- Eudragit™ S dissolving @ pH 6.8, and
- shellac dissolving @ pH 7.2.

- 20 When necessary, the erodable coating may be modified by addition of plasticisers or anti-tack agents. Suitable materials for this purpose include waxy materials such as glycerides, for example glyceryl monostearate.

- 25 Typical sizes for the opening(s), when circular, to be formed in the coating are in the range 0.5 mm – 8 mm of diameter, such as 1, 2, 4 or 4 mm in diameter, depending on the overall size of the tablet and the desired rate of release. The opening(s) may have any convenient geometrical shape, but a rounded shape, e.g. substantially circular or elliptical, is generally preferred. More elaborate shapes, such as text characters or graphics, may also be formed, provided that the release rate can be made uniform in individual dosage forms. Typical sizes of non-circular openings are equivalent in area to
- 30 the above mentioned sizes for circular openings, thus in the range of from about 0.19 to about 50.3 mm².

- 35 For the purposes of the present invention, the term "opening" is synonymous with hole, aperture, orifice, passageway, outlet etc.

- The opening(s) may be formed by methods disclosed in US 5,004,614. Typically opening(s) may be formed by drilling, for example using mechanical drill bits or laser beams, or by punches that remove the cut area. The formation of the opening(s) may by

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default remove a small portion of the exposed core. It is also possible to purposely form a cavity below the aperture as a release rate controlling device, the cavity exposing a greater initial surface area of core than a flat surface. Suitably, the opening(s) extend through the entire erodable coating such that there is immediate exposure of the core to the environmental fluid when the device is placed in the desired environment of use.

Also it is possible to form the opening(s) *in situ* when the dosage form is administered, by forming a coating containing pore-forming agents i.e. material that will dissolve in the stomach to create pores in the coating. Accordingly, there is also provided an oral dosage form comprising,

- (i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and
- (ii) an erodable coating surrounding said core, which coating comprises a pore forming agent that is erodable in the pH range from 1 to 3 to form one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core;

characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the dosage form occurs through the said opening(s) by the erosion of said erodable core and through erosion of said erodable coating under pre-determined pH conditions.

In US 5,004,614, the opening(s) preferably comprise about 10 - 60 % of the total face area of the tablet i.e. the upper and lower surfaces of a biconvex tablet. In the present invention, the opening(s) may comprise 0.25 to 70%, such as 10 - 70% of the total face area.

Alternatively, it may be useful to characterise the rate controlling effect of the opening(s) by reference to the area of the opening(s) relative to the total surface area of the coated tablet. Additionally, especially in cases where the core erodes by undercutting of the edges of the opening(s), the rate controlling effect may be related to the total circumference of the opening(s).

An unexpected finding is that two openings, for example one on each primary surface of a biconvex tablet, release an active agent from the core at a rate marginally greater than that of a single opening of the same overall area. However the variability of the release rate from the two openings is less than the variability of release rate from the corresponding single opening. Therefore, in the preferred embodiment of the invention, the coating of the core is provided with two, or more than two, apertures leading to the

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core. More preferably, the erodable coating surrounding the core is provided with two, or more than two, openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core.

5 Where more than one opening is provided, the openings may be located on the same face of the oral dosage form, or on different faces. Suitably, the oral dosage form has two openings, one on each opposing face. Suitably, the oral dosage form is a tablet having two opposed primary surfaces, each surface having one opening through the coating.

10 As a protection for the core material, to prevent contamination via the opening(s) before dosing, it may be desirable to provide a conventional seal coating to either the core, or to the dosage form after formation of the opening(s). The seal coat may be a sub-coat or over-coat to the erodable coating.

15 By adjustment of the above variables and the surface area of the exposed core, the release rates in the different environmental conditions can be harmonised to obtain comparable release rates under different body environments, and so achieve more constant dosing to a patient.

20 Preferably the dissolution rates of the oral dosage forms of this invention are arranged, for example by routine adjustment of the erodable coating and dimensions of the opening(s), so that the rate of release is substantially uniform in the different pH environments experienced by the dosage form on administration. Dissolution rates may
25 be assessed by *in vitro* testing in solutions of the appropriate pHs. For example, when comparing dissolution in the stomach and intestine, tests may be carried out initially at pH 1.5 with a transfer to pH 6.8 after 2 hours or 4 hours, as an assumed time for residence in the stomach before emptying into the intestines of a notional patient in respectively fasted and fed conditions.

30 The present invention further provides a method for the treatment and/or prophylaxis of disorders in a human or non-human mammal susceptible to treatment by a pharmaceutically acceptable weak base, which comprises administering an oral dosage form of this invention comprising a pharmaceutically acceptable weak base or a
35 pharmaceutically acceptable salt or solvate thereof to a human or non-human mammal in need thereof.

In a preferred embodiment the present invention provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, which method comprises administering an oral dosage form of this invention comprising Compound A or a pharmaceutically acceptable salt or solvate thereof, to a human or non-human mammal in need thereof.

As used herein the term "pharmaceutically acceptable" embraces compounds, compositions and ingredients for both human and veterinary use. For example the term "pharmaceutically acceptable salt" embraces a veterinarily acceptable salt. In particular, suitable pharmaceutically acceptable salted forms of Compound A include those described in European Patent Number 0 306 228 and International Patent Application, Publication Number WO94/05659.

Suitable pharmaceutically acceptable solvates include hydrates.

No adverse toxicological effects are indicated in the above mentioned treatments.

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.

In the following Examples, tablet cores were formed by conventional means by mixing together the active ingredients with excipients and compressing to form the tablet core. These Examples are intended to be by way of illustration rather than limitation of the present invention, and Compound A is used simply as one example of a weak base suitable for use with the present invention.

Example 1

A core was formed from the following formulation:

	%w/w
Compound A (as maleate salt)	7.1
HPMC	30.0
Lactose	60.9
Colloidal silicon dioxide	0.5
Magnesium stearate	1.5

by compression to form 7 mm normal concave tablets of 150 mg.

The tablet cores were coated with a polymethacrylate resin soluble at pH 5.5 to a total weight of 160 mg.

- 5 An opening of diameter 3.0 mm was drilled through the coating in each of the two primary surfaces of the coated cores to expose the surface of the core.**

Example 2

A core was formed from the following formulation:

10		%w/w
	Compound A (as maleate salt)	7.1
	HPMC	20.0
	Lactose	70.9
	Colloidal silicon dioxide	0.5
15	Magnesium stearate	1.5

by compression to form 7 mm normal concave tablets of 150 mg.

20 The tablet cores were coated with a polymethacrylate resin soluble at pH 5.5 to a total weight of 160 mg.

An opening of diameter 3.5 mm was drilled through the coating in each of the two primary surfaces of the coated cores to expose the surface of the core.

- 25 Due to the larger openings and lower HPMC content, the dosage forms of Example 2 exhibited a faster release of Compound A at pH 1.5 and pH 6.8.**

30

35

Dissolution Tests

Figure 1 shows dissolution rates for the formulations of Examples 1 and 2 starting at pH 1.5 with a transfer to pH 6.8 after 4 hours, as an assumed time for residence in the fed stomach before emptying into the intestines. The medium for this dissolution test is initially an aqueous solution of sodium chloride and hydrochloric acid, pH 1.5 to mimic the pH found in the stomach environment. This medium is then titrated to pH 6.8 by the addition of aqueous sodium dodecyl sulfate and an aqueous solution of sodium acetate and tris(hydroxymethyl)methylamine after 4 hours to mimic the pH found in the intestine. Figure 1 shows that with an erodable coat, the release is substantially complete i.e. over 90% release is achieved, after about 8 hours for the formulation of Example 2, and 12 hours for the formulation of Example 1. During that period, the rate of release is substantially uniform at both pHs, for both formulations.

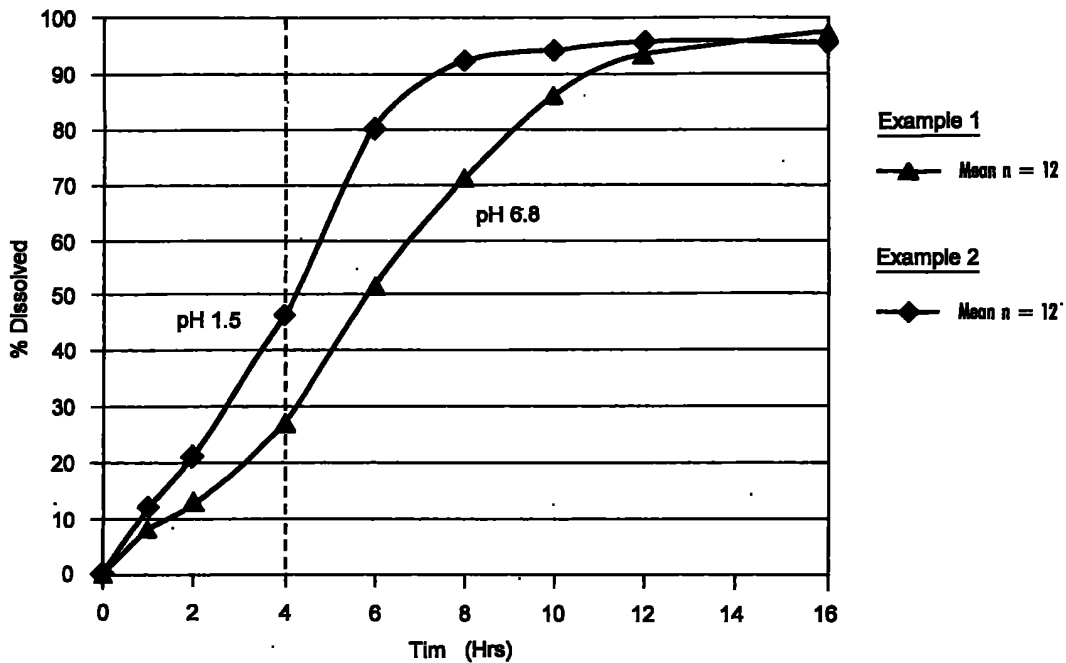
Testing in the same solutions with transfer at 2 hours to mimic gastric emptying in the fasted condition, gave similar results.

Claims

1. An oral dosage form comprising,
5 (i) an erodable core, which core comprises a pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof; and
(ii) an erodable coating around said core, which coating comprises one or more openings extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core;
10 characterised in that release of the pharmaceutically active weak base or a pharmaceutically acceptable salt or solvate thereof from the dosage form occurs through the said opening(s) by the erosion of said erodable core and through erosion of said erodable coating under pre-determined pH conditions.
- 15 2. An oral dosage form according to claim 1 in which the erodable coating erodes at pH > 4.5.
3. An oral dosage form according to claim 1 in which the erodable coating material is selected from polymethacrylate polymers, coprocessed polyvinylacetate phthalate,
20 cellulose acetate trimellitate, cellulose acetate phthalate, shellac, hydroxypropyl-methylcellulose phthalate polymers and their copolymers, and blends thereof.
4. An oral dosage form according to any preceding claim in which the erodable coating has a thickness in the range 0.05 to 0.5 mm.
25
5. An oral dosage form according to any preceding claim in which the opening(s) sizes are in the range 0.5 mm to 8 mm.
6. An oral dosage form according to any preceding claim in which the erodable
30 coating comprises two openings.
7. An oral dosage form according to any preceding claim, in which the erodable core is in a multi-layered form.
- 35 8. An oral dosage form according to any preceding claim in which the opening(s) in the erodable coating comprise about 10 to 70 % of the total face area of the dosage form.

9. An oral dosage form according to any preceding claim in which the core is predominantly hydroxypropylmethyl cellulose and lactose.
10. An oral dosage form according to any preceding claim in which the
5 pharmaceutically acceptable weak base is selected from the Primary Compounds of the invention or a pharmaceutically acceptable salt or solvate thereof.
11. An oral dosage form according to claim 10, in which the pharmaceutically acceptable weak base is 5-[4-[2-(N-methyl-N-(2-
10 pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione ('Compound A') or a pharmaceutically acceptable salt or solvate thereof.
12. A process for the preparation of an oral dosage form according to claim 1, which process comprises:
15 (a) preparing an erodable tablet core;
(b) coating the core with a material with pH-dependent erodability; and
(c) creating one or more openings in the coating, said opening(s) extending substantially completely through said coating but not penetrating said core and communicating from the environment of use to said core.
20
13. A method for the treatment and/or prophylaxis of disorders in a human or non-human mammal susceptible to treatment by a pharmaceutically acceptable weak base, which comprises administering an oral dosage form according to claim 1 comprising a pharmaceutically acceptable weak base or a pharmaceutically acceptable
25 salt or solvate thereof to a human or non-human mammal in need thereof.

Fig. 1



INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/00594

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/44

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)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 01925 A (FORUM CHEMICALS LIMITED) 8 March 1990 (1990-03-08) page 1, line 1 - line 6 page 17, line 2 - line 12 & US 5 004 614 A 2 April 1991 (1991-04-02)	1-13
P,X	WO 02 38131 A (SMITHKLINE BEECHAM P.L.C.) 16 May 2002 (2002-05-16)	12
P,A	page 1, line 1 - page 6, line 15 page 3, line 27 - line 33	1-11,13
A	GB 2 150 830 A (ALZA CORPORATION) 10 July 1985 (1985-07-10) page 4, column 2, line 75 - column 2, line 118 claims 1,6,8	1-13

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

☒ Patent family members are listed in annex.

* 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 document 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.
- "Z" document member of the same patent family

Date of the actual completion of the international search

16 June 2003

Date of mailing of the international search report

25/06/2003

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INTERNATIONAL SEARCH REPORT

Int'l application No.
PCT/GB 03/00594

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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:
Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 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 an additional fee, this Authority did not invite payment of any additional fee.
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.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 03/00594

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9001925 A	08-03-1990	AT 110262 T AU 4218489 A CA 1339079 A1 DE 68917677 D1 DE 68917677 T2 EP 0365123 A1 ES 2058543 T3 WO 9001925 A1 GB 2222948 A , B IE 63764 B1 US 5004614 A	15-09-1994 23-03-1990 29-07-1997 29-09-1994 22-12-1994 25-04-1990 01-11-1994 08-03-1990 28-03-1990 14-06-1995 02-04-1991
WO 0238131 A	16-05-2002	AU 1828002 A WO 0238131 A2	21-05-2002 16-05-2002
GB 2150830 A	10-07-1985	AU 566109 B2 AU 2235483 A CA 1231283 A1 CH 659584 A5 DE 3400496 A1 FR 2560044 A1 JP 1894450 C JP 6023090 B JP 60174713 A	08-10-1987 20-06-1985 12-01-1988 13-02-1987 18-07-1985 30-08-1985 26-12-1994 30-03-1994 09-09-1985

Nueva composición

Campo de la invención

La invención se refiere a una forma de dosificación oral que proporciona liberación controlada de un agente farmacéutico activo en diferentes medios corporales, a un procedimiento para preparar dicha forma de dosificación y al uso de dicha forma de dosificación en medicina.

Antecedentes de la invención

10 El uso de un recubrimiento para controlar la velocidad de liberación de un agente activo ha sido centro de atención y se han desarrollado muchos dispositivos diferentes para tal fin. Por ejemplo, en la solicitud internacional de patente, número de publicación WO 01/05430, se describe un dispositivo de suministro de fármaco que permite el suministro de sustancias farmacológicas que presentan solubilidad dependiente del pH, en particular compuestos que son más solubles a bajos niveles de pH (por debajo de pH 2) que a niveles casi neutros (mayores que aproximadamente pH 5). Tales dispositivos de liberación se caracterizan por la presencia de un recubrimiento que es impermeable e insoluble en el fluido ambiental de uso.

En la solicitud internacional de patente, número de publicación WO 95/30422, se describe una serie de formas de dosificación de liberación controlada de azitromicina. En particular, se describen una serie de formas de dosificación que reducen la exposición del tracto GI superior (es decir, el estómago) a altas concentraciones de azitromicina, por el uso de un recubrimiento dependiente del pH. Tales formas de dosificación no ofrecen aberturas a través de las cuales pueda ocurrir la liberación de la sustancia farmacológica.

La patente de EE.UU. número 6.099.859 describe un comprimido de liberación controlada para el suministro de un fármaco antihiper glucémico, que comprende un núcleo osmóticamente activo que contiene el fármaco y una membrana semipermeable, en el que la membrana semipermeable es permeable al paso de agua y fluidos biológicos y es impermeable al paso de la sustancia farmacológica. La membrana semipermeable contiene al menos una vía para la liberación del fármaco antihiper glucémico.

En la patente de EE.UU. número 5.004.614, se describen dispositivos adicionales.

les que utilizan un recubrimiento para controlar la velocidad de liberación de un agente activo. En esta patente, se describe un núcleo de comprimido provisto de un recubrimiento externo que es sustancialmente impermeable al fluido ambiental. Dicho recubrimiento exterior puede prepararse a partir de materiales que o son insolubles o son solubles en los fluidos ambientales. Cuando se utiliza un material soluble, el recubrimiento es de espesor suficiente para que el núcleo no quede expuesto al fluido ambiental antes de que haya transcurrido la liberación controlada del agente activo. A través de este recubrimiento externo impermeable, se han creado una o más aberturas, de modo que se facilita a los fluidos ambientales una ruta de acceso al núcleo. Por lo tanto, al ser ingerido el comprimido recubierto, el fluido gastrointestinal puede entrar a través de la(s) abertura(s) y entrar en contacto con el núcleo, o penetrar en él, para liberar el agente activo. El resultado es que el agente activo es liberado de manera controlada y solamente por la(s) abertura(s). La geometría preferida es tal que hay un orificio circular en ambas caras superior e inferior del comprimido recubierto. La(s) abertura(s) en cuestión ocupa(n) una superficie que constituye aproximadamente 10 a 60 por ciento de la superficie de las caras del comprimido recubierto. Se encuentra que la velocidad de liberación del fármaco está directamente relacionada con el diámetro de la(s) abertura(s) y con la solubilidad del núcleo matricial y del agente activo, lo que permite la posibilidad de que haya diversos perfiles de liberación de fármacos correspondientes a una liberación de orden cero o de primer orden.

Esta invención se basa en el hallazgo de que los recubrimientos sustancialmente impermeables de la patente de EE.UU. 5.004.614 no son adecuados para la liberación controlada de todos los agentes activos, especialmente de las bases débiles farmacéuticamente activas, o sus sales y solvatos farmacéuticamente aceptables. Tales agentes activos presentan una acusada solubilidad dependiente del pH, es decir, son más solubles a un pH en el entorno de 2, asociado con regiones asentadas en el estómago, si se compara con su solubilidad en las condiciones generalmente neutras del intestino delgado, pH en torno a 7.

Se ha encontrado que, para la administración de una base débil farmacéuticamente activa o una base o solvato de la misma farmacéuticamente aceptable, en que es deseable que la liberación del compuesto activo tenga lugar en más de un medio de pH, es beneficioso que el recubrimiento sea erosionable o soluble de una manera dependen-

te del pH.

Compendio de la invención

Por consiguiente, en su aspecto más amplio la presente invención proporciona una forma de dosificación oral que comprende un núcleo erosionable que contiene una base débil farmacéuticamente activa o una sal o un solvato farmacéuticamente aceptable de la misma, teniendo el núcleo un recubrimiento con una o más aberturas que conducen al núcleo, caracterizado porque el recubrimiento es erosionable en condiciones de pH predeterminadas.

La presente invención proporciona además una forma de dosificación oral, que comprende:

(i) un núcleo erosionable, núcleo que comprende una base débil farmacéuticamente activa o una sal o solvato de la misma farmacéuticamente aceptable; y

(ii) un recubrimiento erosionable en torno a dicho núcleo, recubrimiento que comprende una o más aberturas que se extienden de modo sustancialmente completo a través de dicho recubrimiento pero que no penetran en dicho núcleo y que comunican el medio de uso con dicho núcleo;

caracterizada porque la liberación de la base débil farmacéuticamente activa o de una sal o solvato de la misma farmacéuticamente aceptable a partir del núcleo erosionable ocurre sustancialmente a través de dicha(s) abertura(s) y a través de la erosión de dicho recubrimiento erosionable en condiciones predeterminadas de pH.

Para evitar dudas, tal como se usa aquí la expresión "base débil" significará cualquier base cuyo ácido conjugado tenga un pKa menor que 11,5; de acuerdo con *The Pharmaceutical Handbook*, 19th Edition, 1980. La expresión "base débil farmacéuticamente aceptable" se interpretará en consecuencia. Adecuadamente, las bases débiles farmacéuticamente activas y sus sales o solvatos farmacéuticamente aceptables para uso en la presente invención presentan una marcada solubilidad dependiente del pH. Preferiblemente, las bases débiles farmacéuticamente aceptables o sus sales o solvatos farmacéuticamente aceptables para uso en la presente invención son más solubles en el intervalo de pH de 1 a 3, comparada con su solubilidad en el intervalo de pH de 4,5 a 8. Las bases débiles farmacéuticamente aceptables preferidas o sus sales o solvatos farmacéuticamente aceptables para uso en la presente invención son más solubles en las condi-

ciones ácidas encontradas en el estómago de los mamíferos que en las condiciones casi neutras del intestino de los mamíferos.

Las bases débiles farmacéuticamente activas adecuadas para uso en la presente invención incluyen: 1-(3-Clorofenil)-2-[(1,1-dimetiletil)amino]-1-propanona ("bupropion"), 1,2,3,9-Tetrahydro-9-metil-3-[(2-metil-1H-imidazol-1-il)metil]-4H-carbazol-4-ona ("ondansetron"), (3*S-trans*)-3-[(1,3-Benzodioxol-5-iloxi)metil]-4-(4-fluorofenil)piperidina ("paroxetina"), α^1 -[[1,1-Dimetiletil)amino]metil]-4-hidroxi-1,3-bencenodimetanol ("salbutamol") y sus sales y/o solvatos farmacéuticamente aceptables.

10 La solicitud de patente europea con número de publicación 0306228A1 se refiere a ciertos derivados de tiazolidindiona que se dice que tienen actividad antihiperoglucémica e hipolipidémica. Una tiazolidindiona particular descrita en EP 0306228A1 es 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona (aquí en lo sucesivo 'Compuesto A'). La solicitud internacional de patente con número de publicación WO
15 94/05659 describe ciertas sales del Compuesto A, incluida la sal maleato en el Ejemplo del mismo.

El compuesto A y sus sales o solvatos farmacéuticamente aceptables tienen propiedades farmacéuticas útiles. En particular, se señala que el compuesto A o una sal o solvato del mismo es útil para el tratamiento y/o la profilaxis de la diabetes mellitus, 20 afecciones asociadas con diabetes mellitus y algunas de sus complicaciones.

Una base débil farmacéuticamente activa preferida para uso en la presente invención es el compuesto A o una sal o solvato farmacéuticamente aceptable del mismo. Una base farmacéuticamente activa particularmente preferida para uso en la presente invención es la sal maleato del compuesto A.

25 Una base débil farmacéuticamente activa adicional para uso en la presente invención es valaciclovir o una sal farmacéuticamente aceptable del mismo. Valaciclovir es el éster de L-valina de aciclovir y su nombre químico es L-valinato de 2-[(2-amino-1,6-dihidro-6-oxo-9H-purin-9-il)metoxi]etilo. Una sal preferida de este compuesto es la sal hidrocloreuro, conocida como hidrocloreuro de valaciclovir. Valaciclovir y su sal hidrocloreuro están descritos en la patente de E.E.UU. número 4.957.924 (véase en particular el ejemplo IB), patente europea número EP 0 308 065 B1 (véase en particular el ejemplo IB), y 30 L.M. Beauchamp et al, *Antiviral Chemistry and Chemotherapy*, 3(3), 157-164 (1992) (véase

se en particular la página 162 columna 1), que se incorporan aquí expresamente por referencia. Una forma cristalina anhidra preferida de hidrocloreuro de valaciclovir está descrita en la solicitud internacional de patente con número de publicación WO 96/22291 (que se incorpora aquí íntegramente por referencia); esta forma cristalina anhidra puede definirse, por ejemplo, por tener sustancialmente el patrón de difracción de rayos X a través de polvo de una o más de las figuras 1 a 3 de WO 96/22291. Algunas síntesis de valaciclovir y su sal hidrocloreuro se dan en WO 96/22291, p.ej. véanse los ejemplos 1A/B y 2A/B y las páginas 4-7 de dicho documento.

- Valaciclovir o una de sus sales se puede utilizar en el tratamiento y/o la supresión
- 10 de una infección vírica en un mamífero, tal como un ser humano, en particular una infección vírica causada por el grupo herpes de virus p.ej. virus herpes zoster y/o herpes simplex tipos 1 o 2. Como guía, se dan las siguientes pautas de dosificación, en donde las dosis están calculadas como valaciclovir en forma de base libre:
- (a) tratamiento de episodios de infección por virus herpes simplex tipos 1 and 2: dosis diaria total de aproximadamente 1 o 2 g administrados como 500 mg dos veces al día o 1 g dos veces al día durante 5 a 10 días;
- 15 (b) supresión de recurrencia de infección por virus herpes simplex tipos 1 y 2 (p.ej. herpes genital): dosis diaria total aproximadamente 250 a 1 g (p.ej. 500 mg dos veces al día) durante un mes a diez años, dependiendo del paciente. Como se describe en WO 97/25989
- 20 (documento incorporado aquí por referencia), el valaciclovir o una de sus sales también se puede emplear en la supresión de herpes genital recurrente en un ser humano como una sola dosis diaria de aproximadamente 200 mg a aproximadamente 1000 mg (p.ej. 250 mg, 500 mg o 1000 mg) de valaciclovir o una sal del mismo (calculado como base libre) durante un periodo de tratamiento eficaz, p.ej. durante aproximadamente 2 meses hasta aproximadamente 10 años.
- 25 (c) tratamiento de infecciones por el virus zoster de la varicela (herpes zoster, p.ej. zona): dosis diaria total aproximadamente 3 g administrados como 1 g tres veces al día durante 7 días;
- (d) supresión infecciones por citomegalovirus: dosis diaria total aproximadamente 8 g administrados como 2 g cuatro veces al día; para pacientes transplantados la dosis diaria se administra durante tres a seis meses en el periodo de riesgo; y para pacientes VIH-positivos se administra una dosis diaria como se indica habitualmente para mejorar la
- 30

calidad de vida, por ejemplo durante dos años o más

Adecuadamente, la base débil farmacéuticamente aceptable se selecciona del grupo formado por 1-(3-Clorofenil)-2-[(1,1-dimetiletil)amino]-1-propanona ("bupropion"), 1,2,3,9-Tetrahidro-9-metil-3-[(2-metil-1H-imidazol-1-il)metil]-4H-carbazol-4-
 5 ona ("ondansetron") y (3*S-trans*)-3-[(1,3-Benzodioxol-5-iloxi)metil]-4-(4-fluorofenil)piperidina ("paroxetina"), L-valinato de 2-[(2-amino-1,6-dihidro-6-oxo-9H-purin-9-il)metoxi]etilo ("valaciclovir"), Compuesto A y sus sales y/o solvatos farmacéuticamente aceptables (aquí en lo sucesivo "los compuestos principales de la invención").
 Adecuadamente, la base débil farmacéuticamente aceptable es 1-(3-Clorofenil)-2-[(1,1-
 10 dimetiletil)amino]-1-propanona ("bupropion") o una sal o solvato de la misma farmacéuticamente aceptable. Adecuadamente la base débil farmacéuticamente aceptable es 1,2,3,9-Tetrahidro-9-metil-3-[(2-metil-1H-imidazol-1-il)metil]-4H-carbazol-4-ona ("ondansetron") o una sal o solvato de la misma farmacéuticamente aceptable. Adecuadamente, la base débil farmacéuticamente aceptable es (3*S-trans*)-3-[(1,3-Benzodioxol-
 15 5-iloxi)metil]-4-(4-fluorofenil)piperidina ("paroxetina") o una sal o solvato de la misma farmacéuticamente aceptable. Más adecuadamente, la base débil farmacéuticamente aceptable es L-valinato de 2-[(2-amino-1,6-dihidro-6-oxo-9H-purin-9-il)metoxi]etilo ("valaciclovir"). Lo más adecuadamente, la base débil farmacéuticamente aceptable es el compuesto A o una sal o solvato del mismo farmacéuticamente aceptable.

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Breve descripción de los dibujos

La figura 1 es una gráfica de la disolución en función del tiempo para dos formulaciones de forma de dosificación oral de acuerdo con esta invención..

25 Descripción detallada de la invención

Las bases débiles farmacéuticamente activas típicas para uso en la presente invención son los "compuestos principales" de la invención, en particular el compuesto A o una sal o solvato del mismo farmacéuticamente aceptable. Tales compuestos y sus sales farmacéuticamente aceptables presentan una marcada solubilidad dependiente del
 30 pH, es decir, son más solubles a pH en torno a 2, asociado a regiones encontradas en el estómago, si se compara con su solubilidad en las condiciones generalmente neutras del intestino delgado, pH en torno a 7.

Los compuestos principales de la invención y sus sales y solvatos farmacéuticamente aceptables tienen propiedades farmacéuticas que están bien documentadas (por ejemplo, las farmacopeas británica y de EE.UU., Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (Londres, The Pharmaceutical Press)).

La forma de dosificación oral de esta invención se puede utilizar también para administrar otras bases débiles farmacéuticamente activas con propiedades de disolución similares a las de los "compuestos principales" de esta invención, para tratar trastornos para los que se sabe que están indicadas las bases débiles.

La referencia anterior a que el recubrimiento es erosionable incluye la situación en la que el recubrimiento se disgrega parcial o totalmente, o se disuelve, o se hace poroso, al contacto con un fluido ambiental para permitir que el fluido entre en contacto con el núcleo. Adecuadamente, el recubrimiento se disgrega completamente. Adecuadamente el recubrimiento se disuelve. Adecuadamente el recubrimiento se hace poroso.

Del mismo modo, las referencias a que el núcleo es erosionable incluyen la situación en la que el núcleo se disgrega parcial o totalmente, o se disuelve, o se hace poroso, al contacto con un fluido ambiental para permitir que el fluido entre en contacto con el agente activo. Adecuadamente, el núcleo se disgrega parcialmente. Adecuadamente, el núcleo se disgrega totalmente. Adecuadamente, el núcleo se disuelve. Adecuadamente, el núcleo se hace poroso.

Aunque esta invención ofrece que la erosión del recubrimiento es dependiente del pH, el núcleo puede liberar la base débil farmacéuticamente activa o una sal o solvato de la misma farmacéuticamente aceptable por erosionamiento de una manera no dependiente del pH. Sin embargo, para satisfacer una demanda específica, el núcleo puede ser un material que permita que la erosión o disgregación del núcleo dependiente del pH libere la base débil farmacéuticamente activa o una sal o solvato de la misma da partir de su matriz.

De la manera más adecuada, aunque la base débil farmacéuticamente activa o una sal o solvato de la misma farmacéuticamente aceptable es más soluble en el estómago que en el intestino, el núcleo se formula de modo que sea erosionable prácticamente al mismo nivel en ambas situaciones.

Para que la(s) abertura(s) en el recubrimiento retenga(n) su integridad y contro-

len la velocidad de liberación, es deseable que la erosión del recubrimiento dependiente del pH tenga un umbral definido, es decir, que el recubrimiento no se erosione sustancialmente salvo en el intestino. Así, se considera que la erosión del recubrimiento tiene un umbral de pH predeterminado y definido al cual se disuelve. Preferiblemente, el recubrimiento se erosiona a $\text{pH} > 4.5$. Más preferiblemente, el recubrimiento se erosiona en el intervalo de pH de 4.5 a 8. Con la mayor preferencia el recubrimiento se erosiona en el intervalo de pH de 5 a 7.

La presente invención encuentra uso particular en la situación en la que el recubrimiento se erosiona en las condiciones de pH del intestino. Por consiguiente, la presente invención también proporciona una forma de dosificación oral que comprende un núcleo erosionable que contiene una base débil farmacéuticamente activa o una sal farmacéuticamente aceptable de la misma, teniendo el núcleo un recubrimiento con una o más aberturas que comunican con el núcleo, caracterizada porque el recubrimiento es erosionable en las condiciones de pH reinantes en el intestino de los mamíferos.

Se apreciará que el uso de un recubrimiento que se erosiona a $\text{pH} > 4.5$ restringirá la cantidad de fármaco liberada en las condiciones ácidas asociadas con el estómago, ya que la liberación ocurre a niveles bajos de pH y está sustancialmente limitada a la difusión del agente activo a través de la(s) abertura(s) del recubrimiento erosionable. Así pues, la presente invención está indicada para solucionar el problema de la "evacuación rápida de la dosis" en el estómago para compuestos que son más solubles en el intervalo de pH de 1 a 3 que en el intervalo de pH de 4.5 a 8. Ya que la forma de dosificación abandona un ambiente de bajo pH y encuentra luego un pH ambiental más alto, p.ej. se desplaza del estómago al intestino, el recubrimiento empezará a disolverse y erosionarse para dejar expuesto todo el núcleo del comprimido. Durante la erosión del recubrimiento, aumenta la superficie disponible para liberar fármaco. La disminución de solubilidad del fármaco y, por lo tanto, de la velocidad de adsorción en el intestino se puede compensar con el aumento de la superficie, debido a que todas las caras del núcleo del comprimido van quedando expuestas a la erosión. El resultado es un perfil de liberación más equilibrado del fármaco en ambos ambientes.

Al aplicar los conceptos de esta invención, la base débil farmacéuticamente activa o una sal o solvato farmacéuticamente aceptable de la misma se puede incorporar en un comprimido oral convencional o en una matriz de liberación controlada (utilizando

tanto un sistema expandible como un sistema no expandible). La matriz se convierte en núcleos que después se recubren con un material con erosionabilidad dependiente del pH, por ejemplo un recubrimiento soluble a $\text{pH} > 4,5$, tal como un copolímero de polimetacrilato. Se pueden taladrar una o más aberturas a través de los recubrimientos utilizando técnicas convencionales como las descritas en la patente de EE.UU. 5.004.614.

De acuerdo con un aspecto adicional de la presente invención, se proporciona un procedimiento para la preparación de una forma de dosificación según la presente invención, cuyo procedimiento comprende:

- (a) preparar un núcleo de comprimido erosionable;
- 10 (b) recubrir el núcleo con un material con erosionabilidad dependiente del pH; y
- (c) crear una o más aberturas en el recubrimiento, extendiéndose dicha(s) abertura(s) sustancialmente en su totalidad a través de dicho recubrimiento pero sin penetrar en dicho núcleo y comunicando el ambiente de uso con dicho núcleo.

El núcleo se puede preparar prensando los ingredientes adecuados para formar una masa compacta que comprende el núcleo de la forma de dosificación (llamado aquí también "núcleo del comprimido". Este se puede preparar utilizando excipientes convencionales para comprimidos y métodos convencionales de prensado de formulaciones. Así, el núcleo típicamente comprende el agente activo o agentes junto con excipientes que imparten características satisfactorias de procesamiento y prensado tales como diluyentes, aglutinantes y lubricantes. Excipientes adicionales que pueden formar parte del núcleo del dispositivo incluyen disgregantes, aromatizantes, colorantes, agentes modificadores de la liberación y/o agentes solubilizantes tales como tensioactivos, modificadores del pH y vehículos de complejación.

Los materiales adecuados para el núcleo incluyen resinas de polimetacrilato erosionables tales como la serie Eudragit™, por ejemplo Eudragit™ L30D, sacarosas, por ejemplo lactosa y maltosa, y ésteres de celulosa, por ejemplo, metilcelulosa, hidroxipropilmetilcelulosa (HPMC) e hidroxipropilcelulosa. Adecuadamente, el núcleo es predominantemente hidroxipropilmetilcelulosa y lactosa. Más adecuadamente, el núcleo consiste esencialmente en hidroxipropilmetilcelulosa, lactosa, dióxido de silicio coloidal y estearato de magnesio.

Típicamente, el agente activo y los excipientes se mezclan a fondo antes de prensarlos para formar un núcleo sólido. El núcleo del dispositivo se puede formar por

métodos de granulación por vía húmeda, métodos de granulación por vía seca o por compresión directa. El núcleo se puede producir de acuerdo con cualquier forma preseleccionada adecuada, tal como una forma biconvexa, semiesférica, casi semiesférica, redonda, ovalada, generalmente elipsoidal, oblonga generalmente cilíndrica o poliédrica, p.ej. una forma de prisma triangular. La expresión "casi semi-esférica" se debe entender de la manera descrita en la patente de EE.UU. 5.004.614. Adecuadamente, el núcleo se formula en una forma biconvexa, p.ej. una que tenga dos superficies opuestas en forma de domo. Además, el núcleo se puede producir en una forma que consta de varias capas (por ejemplo, de dos o tres capas).

10 La cantidad de base débil farmacéuticamente activa o de una sal o solvato farmacéuticamente aceptable de la misma, presente dentro del núcleo es una cuestión que se determinará en base a consideraciones farmacéuticas típicas, p.ej. dosis conocidas para la base débil farmacéuticamente activa o una sal o solvato farmacéuticamente aceptable de la misma, y no está limitada por el procedimiento de esta invención.

15 En particular, cuando el compuesto A o una sal o solvato del mismo farmacéuticamente aceptable se utiliza de acuerdo con la presente invención, un intervalo adecuado de dosificación es 2 a 12 mg. Así, formas de dosificación adecuadas comprenden 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 o 12 mg de compuesto A o una sal o solvato farmacéuticamente aceptable del mismo.

20 Formas de dosificación particulares comprenden 2 a 4 mg de compuesto A o una sal o solvato farmacéuticamente aceptable del mismo.

Formas de dosificación particulares comprenden 4 a 8 mg de compuesto A o una sal o solvato farmacéuticamente aceptable del mismo.

25 Formas de dosificación particulares comprenden 8 a 12 mg de compuesto A o una sal o solvato farmacéuticamente aceptable del mismo.

Una forma de dosificación comprende 2 mg de compuesto A o una sal o solvato farmacéuticamente del mismo.

Formas de dosificación preferidas comprenden 4 mg de compuesto A o una sal o solvato farmacéuticamente aceptable del mismo.

30 Formas de dosificación preferidas comprenden 8 mg de compuesto A o una sal o solvato farmacéuticamente aceptable del mismo.

El núcleo se puede recubrir con un material adecuado erosionable dependiendo

del pH por cualquier método de recubrimiento farmacéuticamente aceptable. Ejemplos incluyen métodos de recubrimiento descritos en la patente de EE.UU. 5.004.614 y el recubrimiento pelicular, recubrimiento con azúcar, recubrimiento por pulverización, recubrimiento por inmersión, recubrimiento por compresión, recubrimiento electrostático. Los métodos típicos incluyen pulverización del recubrimiento sobre el núcleo del comprimido en una unidad de artesa rotatoria, o en una unidad de lecho fluidizado hasta que se obtiene el espesor deseado de recubrimiento. Adecuadamente, el recubrimiento añade aproximadamente $4 - 8 \text{ mg/cm}^2$ o $5 - 7 \text{ mg/cm}^2$ de polímero seco en torno a la superficie del comprimido. Típicamente esto da como resultado un incremento en peso (respecto del núcleo) de $3 - 10\%$ o $5 - 10\%$ en peso. Adecuadamente, el recubrimiento tiene un espesor en el intervalo de 0,05 a 0,5 mm.

Los materiales y sus mezclas adecuados para uso como material de recubrimiento erosionable dependiente del pH en esta invención incluyen diversos polímeros de polimetacrilato, poli(acetato-ftalato de vinilo) coprocesado, acetato-trimelitato de celulosa, acetato-ftalato de celulosa, laca, polímeros de ftalato de hidroxipropilmetilcelulosa y sus copolímeros.

El material de recubrimiento se selecciona adecuadamente para que sea insoluble en los ácidos del estómago, es decir, a pH 1,5-2, y sea soluble o erosionable en el intestino delgado, es decir en torno a pH 5,5 o en el intestino grueso, es decir, en torno a pH 7. Para conseguir esto, típicamente el material del recubrimiento es erosionable a pH 4,5 o superior.

Adecuadamente, el material de recubrimiento se selecciona entre:

- acetato trimelitato de celulosa (CAT) que se disuelve a pH 4,8,
- poli(acetato-ftalato de vinilo) que se disuelve a pH 5,0,
- ftalato de hidroxipropilmetilcelulosa 50 que se disuelve a pH 5,2,
- ftalato de hidroxipropilmetilcelulosa 55 que se disuelve a pH 5,4,
- Acryl-eze™ que se disuelve a pH 5,5,
- Aquateric™ que se disuelve a H 5,8,
- acetato ftalato de celulosa que se disuelve a pH 6,0,
- Eudragit™ L30 D que se disuelve a pH 5,5,
- Eudragit™ L que se disuelve a pH 6,0,
- Eudragit™ S que se disuelve a pH 6,8, y

laca que se disuelve a pH 7,2.

Cuando sea necesario, el recubrimiento erosionable se puede modificar por adición de plastificantes o agentes anti-pegajosos. Los materiales adecuados para este fin incluyen materiales cerosos tales como los glicéridos, por ejemplo monoestearato de glicerilo.

Los tamaños típicos para la(s) abertura(s) que se forman en el recubrimiento están en el intervalo de 0,5 mm – 8 mm de diámetro, tal como 1, 2, 3 o 4 mm de diámetro, dependiendo del tamaño total del comprimido y de la velocidad deseada de liberación. La(s) abertura(s) pueden tener cualquier forma geométrica conveniente, pero generalmente se prefiere una forma redondeada, por ejemplo, sustancialmente circular o elíptica. También se pueden fabricar formas más elaboradas tales como caracteres tipográficos o gráficos, siempre que la velocidad de liberación pueda uniformizarse en las formas individuales de dosificación. Los tamaños típicos de aberturas no circulares son equivalentes en superficie a los tamaños citados anteriormente para aberturas circulares, estando pues en el intervalo de aproximadamente 0,19 a aproximadamente 50,3 mm.

Para los fines de la presente invención, el término "abertura" es sinónimo de agujero, apertura, orificio, vía de paso, salida, etc.

La(s) abertura(s) se pueden formar por los métodos descritos en la patente de EE.UU. 5.004.614. Típicamente, la(s) abertura(s) se pueden formar por taladro, por ejemplo, utilizando brocas mecánicas o rayos láser, o con sacabocados, que retiran la superficie cortada. La formación de la(s) abertura(s) puede, retirar por defecto una pequeña porción del núcleo expuesto. También es posible formar intencionadamente una cavidad bajo la abertura como dispositivo controlador de la velocidad de liberación, exponiendo así la cavidad una superficie inicial del núcleo mayor que si se tratara de una superficie plana. Adecuadamente, la(s) abertura(s) se extienden a través de todo el recubrimiento erosionable, de manera que haya una exposición inmediata del núcleo al fluido ambiental cuando el dispositivo se pone en el ambiente deseado de uso.

También es posible formar la(s) abertura(s) *in situ* cuando se administra la forma de dosificación si se forma un recubrimiento que contiene agentes formadores de poros, es decir, material que se disolverá en el estómago para crear poros en el recubrimiento. Por consiguiente, también se proporciona una forma de dosificación que comprende:

(i) un núcleo erosionable, núcleo que comprende una base débil farmacéuticamente ac-

tiva o una sal o solvato farmacéuticamente aceptable de la misma; y
(ii) un recubrimiento erosionable rodeando a dicho núcleo, recubrimiento que comprende un agente formador de poros que es erosionable en el intervalo de pH de 1 a 3 para formar una o más aberturas que se extienden sustancialmente por la totalidad de dicho recubrimiento pero sin penetrar en dicho núcleo y que comunican con el ambiente de uso de dicho núcleo;
caracterizada porque la liberación de la base débil farmacéuticamente activa o de una sal o solvato farmacéuticamente aceptable de la misma a partir de la forma de dosificación ocurre a través de dichas abertura(s) por la erosión de dicho núcleo erosionable y mediante la erosión de dicho recubrimiento erosionable en condiciones predeterminadas de pH.

En la patente de EE.UU. 5.004.614, las abertura(s) preferiblemente representan aproximadamente 10 - 60 % de la superficie total de las caras del comprimido, es decir de las superficies superior e inferior de un comprimido biconvexo. En la presente invención, la(s) abertura(s) pueden representar 0,25 a 70%, tal como 10 - 70% de la superficie total de las caras.

Alternativamente, puede ser útil caracterizar el efecto de la(s) abertura(s) para controlar la velocidad por referencia a la superficie que ocupa(n) la(s) abertura(s) en relación con la superficie total del comprimido recubierto. Adicionalmente, especialmente en los casos en que el núcleo se erosiona socavando los bordes de la(s) abertura(s), el efecto controlador de la velocidad puede estar relacionado con la circunferencia total de la(s) abertura(s).

Un hallazgo inesperado es que dos aberturas, por ejemplo una en cada superficie principal de un comprimido biconvexo, liberan un agente activo a partir del núcleo a una velocidad marginalmente mayor que la de una sola abertura de la misma superficie total. Sin embargo, la variabilidad de la velocidad de liberación a partir de las dos aberturas es menor que la variabilidad de la velocidad de liberación a partir de una sola abertura correspondiente. Por lo tanto, en la realización preferida de la invención, el recubrimiento del núcleo está provisto de dos, o más de dos, aberturas que llegan al núcleo. Más preferiblemente, el recubrimiento erosionable que rodea al núcleo está provisto de dos, o más de dos, aberturas que se extienden de modo sustancialmente completo a través de dicho recubrimiento, pero que no penetran en dicho núcleo, y que comunican el

ambiente de uso con dicho núcleo.

Cuando se proporciona más de una abertura, las aberturas pueden estar localizadas en la misma cara de la forma de dosificación oral o en caras diferentes. Adecuadamente, la forma de dosificación oral tiene dos aberturas, una en cada cara opuesta.

5 Adecuadamente, la forma de dosificación oral es un comprimido que tiene dos superficies principales opuestas, teniendo cada superficie una abertura a través del recubrimiento.

10 Como protección del material del núcleo, para prevenir la contaminación a través de la(s) abertura(s) antes de la dosificación, puede ser deseable proporcionar un recubrimiento hermético, ya sea sobre el núcleo o sobre la forma de dosificación tras la formación de la(s) abertura(s). El recubrimiento hermético puede ser un recubrimiento inferior o un recubrimiento superior en relación con el recubrimiento erosionable.

15 Se pueden armonizar las velocidades de liberación en las diferentes condiciones ambientales ajustando las variables anteriores y la superficie del comprimido expuesto, para obtener velocidades de liberación comparables en ambientes corporales diferentes, y así conseguir una dosificación más constante para un paciente.

20 Preferiblemente las velocidades de disolución de las formas orales de dosificación de esta invención se disponen, por ejemplo, por ajuste rutinario del recubrimiento erosionable y de las dimensiones de la(s) abertura(s), de modo que la velocidad de liberación sea sustancialmente uniforme en los diferentes ambientes de pH experimentados por la forma de dosificación cuando es administrada. Las velocidades de disolución se pueden evaluar por ensayo *in vitro* en soluciones de los pH apropiados. Por ejemplo, cuando se comparan las disoluciones en el estómago y en el intestino, se pueden llevar a cabo inicialmente ensayos a pH 1,5 con una transferencia a pH 6,8 después de 2 horas o 25 4 horas, como tiempo asumido de permanencia en el estómago antes de evacuar al intestino de un paciente imaginario en condiciones de respectivas de ayuno y comida.

30 La presente invención proporciona además un método para el tratamiento y/o la profilaxis de trastornos en un ser humano u otros mamíferos susceptibles de ser tratados con una base débil farmacéuticamente aceptable, que comprende administrar una forma de dosificación oral de esta invención que comprende una base débil farmacéuticamente aceptable o una sal o solvato farmacéuticamente aceptable de la misma a un ser humano u otro mamífero en necesidad de ello.

En una realización preferida, la presente invención proporciona un método para tratamiento y/o profilaxis de diabetes mellitus, afecciones asociadas con diabetes mellitus y algunas de sus complicaciones, cuyo método comprende administrar una forma de dosificación oral de esta invención que comprende el compuesto A o una sal o solvato farmacéuticamente aceptable del mismo, a un ser humano u otro mamífero en necesidad de ello.

Tal como se utiliza aquí "farmacéuticamente aceptable" abarca compuestos, composiciones e ingredientes tanto para uso en medicina humana como veterinaria. Por ejemplo, "la expresión "sal farmacéuticamente aceptable" abarca una sal veterinariamente aceptable. En particular, las formas salificadas farmacéuticamente aceptables y adecuadas del compuesto A incluyen las descritas en la patente europea número 0306228 y en la solicitud internacional de patente con número de publicación WO94/05659.

Los solvatos farmacéuticamente aceptables y adecuados incluyen los hidratos. No hay indicación de efectos toxicológicos adversos en los tratamientos mencionados anteriormente.

Todas las publicaciones, incluidas pero sin limitación las patentes y las solicitudes de patentes citadas en esta memoria descriptiva se incorporan aquí por referencia, como si se hubiera indicado de modo específico e individual que cada publicación individual se incorpora aquí por referencia como si estuviera descrita íntegramente.

En los siguientes ejemplos, se formaron núcleos de comprimidos por medios convencionales mezclando conjuntamente los ingredientes activos con excipientes y prensando para formar el núcleo del comprimido. Se pretende que estos ejemplos sirvan de ilustración pero no de limitación de la presente invención, y el compuesto A se utiliza simplemente como un ejemplo de base débil adecuada para uso con la presente invención.

Ejemplo 1

Se formó un núcleo a partir de la siguiente formulación

30

	% peso/peso
Compuesto A (como sal maleato)	7,1

HPMC	30,0
Lactosa	60,9
Dióxido de silicio coloidal	0,5
Estearato de magnesio	1,5

5

por prensado para formar comprimidos cóncavos normales de 7 mm y 150 mg.

Los núcleos de los comprimidos se revistieron con resina de polimetacrilato, soluble a pH 5,5, hasta un peso total de 160 mg.

Se taladró una abertura de 3,5 mm de diámetro a través del revestimiento en cada una de las dos caras principales de los comprimidos revestidos para exponer la superficie del núcleo.

Ejemplo 2

Se formó un núcleo a partir de la siguiente formulación:

15

	% peso/peso
Compuesto A (como sal maleato)	7,1
HPMC	20,0
Lactosa	70,9
20 Dióxido de silicio coloidal	0,5
Estearato de magnesio	1,5

por prensado para formar comprimidos cóncavos normales de 7 mm y 150 mg.

Los núcleos de los comprimidos se revistieron con resina de polimetacrilato, soluble a pH 5,5, hasta un peso total de 160 mg.

Se taladró una abertura de 3,0 mm de diámetro a través del revestimiento en cada una de las dos caras principales de los comprimidos revestidos para exponer la superficie del núcleo.

Debido al mayor tamaño de las aberturas y al menor contenido de HPMC, las formas de dosificación del Ejemplo 2 presentaron una liberación más rápida de compuesto A a pH 1,5 y pH 6,8.

30

Ensayos de dilución

- La Figura 1 muestra velocidades de disolución para las formulaciones de los ejemplos 1 y 2, partiendo de pH 1,5 con una transferencia a pH 6,8 después de 4 horas, como presunto tiempo de residencia en el estómago con comida antes de evacuarla al
- 5 intestino. El medio para este ensayo de disolución es inicialmente una solución acuosa de cloruro de sodio y ácido clorhídrico, pH 1,5 para simular el pH encontrado en el ambiente del estómago. Este medio se valora después a pH 6,8 por adición de dodecilsulfato de sodio acuoso y de una solución acuosa de acetato de sodio y tris(hidroximetil)metilamina después de 4 horas, para simular el pH encontrado en el
- 10 intestino. La Figura 1 muestra que con un recubrimiento erosionable, la liberación es sustancialmente completa, es decir, se consigue más de 90% de liberación, después de aproximadamente 8 horas para la formulación del Ejemplo 2, y 12 horas para la formulación del Ejemplo 1. Durante ese periodo, la velocidad de liberación es sustancialmente uniforme a ambos valores de pH, para ambas formulaciones.
- 15 El ensayo en las mismas soluciones con transferencia en 2 horas para simular evacuación gástrica en situación de ayunas, dio resultados similares.

REIVINDICACIONES

1. Una forma de dosificación oral, que comprende:
 - (i) un núcleo erosionable, núcleo que comprende una base débil farmacéuticamente activa o una sal o solvato de la misma farmacéuticamente aceptable; y
 - (ii) un recubrimiento erosionable en torno a dicho núcleo, recubrimiento que comprende una o más aberturas que se extienden de modo sustancialmente completo a través de dicho recubrimiento pero que no penetran en dicho núcleo y que comunican el medio de uso con dicho núcleo;
- 10 caracterizada porque la liberación de la base débil farmacéuticamente activa o de una sal o solvato de la misma farmacéuticamente aceptable a partir de la forma de dosificación ocurre sustancialmente a través de dicha(s) abertura(s) por erosión de dicho núcleo erosionable y a través de la erosión de dicho recubrimiento erosionable en condiciones predeterminadas de pH.
- 15
2. Una forma de dosificación oral según la reivindicación 1, en la que el recubrimiento erosionable se erosiona $\text{pH} > 4,5$.
3. Una forma de dosificación oral según la reivindicación 1, en la que el
- 20 material de recubrimiento erosionable se selecciona entre polímeros de polimetacrilato, poli(acetato-ftalato de vinilo) coprocesado, acetato-trimelitato de celulosa, acetato-ftalato de celulosa, laca, polímeros de ftalato de hidroxipropilmetilcelulosa y sus copolímeros, y mezclas de ellos.
- 25
4. Una forma de dosificación oral según cualquier reivindicación precedente, en la que el revestimiento erosionable tiene un espesor en el intervalo de 0,05 a 0,5 mm.
5. Una forma de dosificación oral según cualquier reivindicación pre-
- 30 cedente, en la que los tamaños de la(s) abertura(s) están en el intervalo de 5 mm a 8 mm.

7. Una forma de dosificación oral según cualquier reivindicación precedente, en la que el recubrimiento erosionable comprende dos aberturas.

8. Una forma de dosificación oral según cualquier reivindicación precedente, en la que el núcleo erosionable está en una forma que consta de varias capas.

9. Una forma de dosificación oral según cualquier reivindicación precedente, en la que la(s) abertura(s) en el recubrimiento erosionable representan aproximadamente 10 a 70 % de la superficie total de las caras de la forma de dosificación.

10. Una forma de dosificación oral según cualquier reivindicación precedente, en la que el núcleo es predominantemente hidroxipropilmetilcelulosa y lactosa.

11. Una forma de dosificación oral según cualquier reivindicación precedente, en la que la base débil farmacéuticamente aceptable se selecciona entre los "compuestos principales" de la invención o una sal o solvato farmacéuticamente aceptable de los mismos.

12. Una forma de dosificación según la reivindicación 11, en la que la base débil farmacéuticamente aceptable es 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona ('compuesto A') o una sal o solvato farmacéuticamente aceptable de la misma.

13. Un procedimiento para la preparación de una forma de dosificación oral según la reivindicación 1, cuyo procedimiento comprende:

- (a) preparar un núcleo de comprimido erosionable;
- (b) recubrir el núcleo con un material con erosionabilidad dependiente del pH; y
- (c) crear una o más aberturas en el recubrimiento, extendiéndose dicha(s) abertura(s) sustancialmente por la totalidad de dicho recubrimiento pero sin penetrar en dicho núcleo y comunicando el ambiente de uso con dicho núcleo.

14. Un método para el tratamiento y/o la profilaxis de trastornos en seres

- 20 -

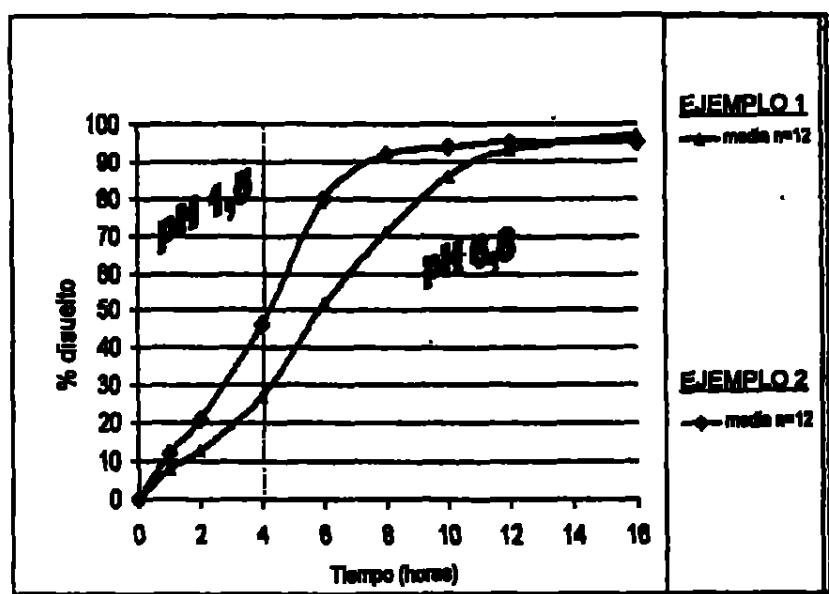
humanos u otros mamíferos susceptibles de ser tratados con una base débil farmacéuticamente aceptable, que comprende administrar una forma de dosificación oral según la reivindicación 1 que comprende una base débil farmacéuticamente aceptable o una sal o solvato farmacéuticamente aceptable de la misma a un ser humano u otro mamífero en
5 necesidad de ello.

RESUMEN

Una forma de dosificación oral, que comprende:

- (i) un núcleo erosionable, núcleo que comprende una base débil farmacéuticamente activa o una sal o solvato de la misma farmacéuticamente aceptable; y
 - 5 (ii) un recubrimiento erosionable rodeando a dicho núcleo, recubrimiento que comprende una o más aberturas que se extienden de modo sustancialmente completo a través de dicho recubrimiento pero que no penetran en dicho núcleo y que comunican el medio de uso con dicho núcleo;
- caracterizada porque la liberación de la base débil farmacéuticamente activa o de una
- 10 sal o solvato de la misma farmacéuticamente aceptable a partir de la forma de dosificación ocurre sustancialmente por erosión de dicho núcleo erosionable y a través de dicha(s) abertura(s) y a través de la erosión de dicho recubrimiento erosionable en condiciones predeterminadas de pH; un procedimiento para preparar dicha forma de dosificación y el uso de dicha forma de dosificación en medicina.

Figura 1



PCT REQUEST

LLK/P32984

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0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/ROH01 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.06.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United Kingdom Patent Office (RO/GB)
0-7	Applicant's or agent's file reference	LLK/P32984
I	Title of invention	NOVEL COMPOSITION
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	GLAXO GROUP LIMITED
II-5	Address:	Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 0NN United Kingdom
II-6	State of nationality	GB
II-7	State of residence	GB
II-8	Telephone No.	+44 20 8047 5000
II-9	Facsimile No.	+44 20 8047 6894
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
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III-1-4	Name (LAST, First)	MARTINI, Luigi
III-1-5	Address:	GlaxoSmithKline New Frontiers Science Park South Third Avenue Harlow, Essex CM19 5AW United Kingdom
III-1-6	State of nationality	GB
III-1-7	State of residence	GB

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LLKP32984

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III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	RE, Vincenzo
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III-2-7	State of residence	GB
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
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III-3-4	Name (LAST, First)	LI, Chi, Leung
III-3-5	Address:	GlaxoSmithKline New Frontiers Science Park South Third Avenue Harlow, Essex CM19 5AW United Kingdom
III-3-6	State of nationality	GB
III-3-7	State of residence	GB
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	WILLY, Helen, Anne
III-4-5	Address:	GlaxoSmithKline New Frontiers Science Park South Third Avenue Harlow, Essex CM19 5AW United Kingdom
III-4-6	State of nationality	GB
III-4-7	State of residence	GB

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IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/have been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	GIDDINGS, Peter, John
IV-1-2	Address:	GlaxoSmithKline Corporate Intellectual Property CN925.1 980 Great West Road Brentford, Middlesex TW8 9GS United Kingdom
IV-1-3	Telephone No.	+44 20 8047 4414
IV-1-4	Facsimile No.	+44 20 8047 6894
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GE GM KE LS MW NZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE BG CH<LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH<LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MY NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

PCT REQUEST

LLK/P32884

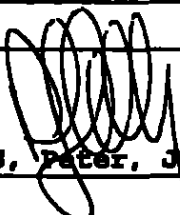
Original (for SUBMISSION) - printed on 12.02.2003 12:03:15 PM

V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.8(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-6	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	12 February 2002 (12.02.2002)
VI-1-2	Number	0203296.9
VI-1-3	Country	GB
VI-2	Priority claim of earlier national application	
VI-2-1	Filing date	12 February 2002 (12.02.2002)
VI-2-2	Number	0203297.7
VI-2-3	Country	GB
VI-3	Priority claim of earlier national application	
VI-3-1	Filing date	12 February 2002 (12.02.2002)
VI-3-2	Number	0203298.5
VI-3-3	Country	GB
VI-4	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2, VI-3
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)
VIII	Declarations	Number of declarations
VIII-1	Declaration as to the identity of the inventor	-
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-

PCT REQUEST

LLK/P32984

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IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	5	-
IX-2	Description	15	-
IX-3	Claims	2	-
IX-4	Abstract	1	EXABST00.TXT
IX-5	Drawings	1	-
IX-7	TOTAL	24	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	reference no. PCT/GB02/05716	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name (LAST, First)	GIDDINGS, Peter, John	

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

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11-1	Date of receipt of the record copy by the International Bureau	
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PATENT COOPERATION TREATY

11 NOV 2003-300054

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

To: THOMPSON, Clive Brentford GLAXOSMITHKLINE Corporate Intell. Property (CN925.1) 980 Great West Road Brentford, Middlesex TW9 9GS GRANDE BRETAGNE		Received - 7 NOV 2003	Date of mailing (day/month/year) 05.11.2003
Applicant's or agent's file reference LLKP32984		IMPORTANT NOTIFICATION	
International application No. PCT/GB03/00594	International filing date (day/month/year) 12.02.2003	Priority date (day/month/year) 12.02.2002	
Applicant GLAXO GROUP LIMITED et al.			

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2339 - 0 Tlx 523858 epmu d Fax +49 89 2339 - 4485	Authorized Officer Hutterer, G Tel. +49 89 2339-8086	
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Form PCT/PEA/416 (July 1992)

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LLKP32984	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA18)	
International application No. PCT/GB03/00594	International filing date (day/month/year) 12.02.2003	Priority date (day/month/year) 12.02.2002
International Patent Classification (IPC) or both national classification and IPC A61K944		
Applicant GLAXO GROUP LIMITED et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 6 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 08.08.2003	Date of completion of this report 05.11.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80299 Munich Tel. +49 89 2369 - 0 Tlx 523855 epmu d Fax: +49 89 2369 - 4445	Authorized Officer Merkl, B Telephone No. +49 89 2369-2138 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB03/00594

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17);*

Description, Pages

1-15 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/1 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/GB03/00594**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. 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. 13

because:

☒ the said international application, or the said claims Nos. 13 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. Statement**

Novelty (N)	Yes: Claims	1-13
	No: Claims	
Inventive step (IS)	Yes: Claims	1-13
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-12 (see item III on separate sheet)
	No: Claims	

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB03/00594**

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB03/00594

Item III:

For the assessment of the present claim 13 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Rule 67.1(iv) PCT, Article 34(4)(a)(i) PCT).

Item V:

D1: WO 90 01925 A (FORUM CHEMICALS LIMITED) 8 March 1990 (1990-03-08) & US 5 004 614 A 2 April 1991 (1991-04-02)

D2: WO 02 38131 A (SMITHKLINE BEECHAM P.L.C.) 16 May 2002 (2002-05-16)

D3: GB-A-2 150 830 (ALZA CORPORATION) 10 July 1985 (1985-07-10)

D1 discloses a controlled release device with an impermeable coating having an orifice for release of drugs. This kind of release device resembles the device disclosed in US-A-5004614 as cited in the description of the pending application wherein the drawbacks of said US patent shall be overcome. According to the present description said device is not suitable for weak base pharmaceutical drugs.

D2 has a priority date and filing date before the priority date of the pending application. However, as the priority date of the pending application is before the publication date of D2, said document does not represent prior art for the purposes of the PCT.

D3 discloses an osmotic drug dispenser having a semi-permeable-enteric wall surrounding a drug formulation. In contrast thereto the device of the pending application has an erodible coating.

The problem the pending application tries to overcome is the controlled release of

INTERNATIONAL PRELIMINARY International application No. PCT/GB03/00594
EXAMINATION REPORT - SEPARATE SHEET

pharmaceutically active weak bases. The cited prior art does not address said problem. Therefore there was no hint for the skilled person to use the device as defined in the claims of the pending application in order to solve the posed problem.

PATENT COOPERATION TREATY

- 0000161

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

GlaxoSmithKline
Corporate IP
RECEIVED BRENTFORD

03 APR 2003

ATTN: LK ADMIN

To:

GIDDINGS, Peter, John
GlaxoSmithKline
Corporate Intellectual Property
CN925.1
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom

Date of mailing (day/month/year)
17 March 2003

UPDATED ON:
07.03.03

CHECKED FILE

COA

IMPORTANT NOTIFICATION

Applicant's or agent's file reference
LLK/P32984

International application No.
PCT/GB03/00594

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

GLAXO GROUP LIMITED (for all designated States except US)
MARTINI, Luigi et al (for US)

International filing date : 12 February 2003 (12.02.03) ✓
Priority date(s) claimed : 12 February 2002 (12.02.02)
12 February 2002 (12.02.02)
12 February 2002 (12.02.02)

Date of receipt of the record copy
by the International Bureau : 07 March 2003 (07.03.03)

List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,
EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

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

Facsimile No. (41-22) 338.88.85

Authorized officer:

Evelyne HUCHON

Telephone No. (41-22) 338 8010

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 17 March 2003 (17.03.03)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference LLK/P32984	International application No. PCT/GB03/00594

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the International application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase - see updated Important Information (as of April 2002)
- ☒ confirmation of precautionary designations (if applicable)
- ☒ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office where a demand for international preliminary examination is filed before the expiration of 18 months from the priority date (see Article 38(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 18828, 18832 and 18834, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette ("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume IA, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.8(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.8(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.8(c) before the expiration of 16 months from the priority date (this time limit may not be extended). If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. The Notice of confirmation and payment must reach the receiving Office within the 16-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 18 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 18-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 18-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

- 4-1110-164

From the INTERNATIONAL BUREAU



 PCT

 20/5/03

 NOTIFICATION CONCERNING

 SUBMISSION OR TRANSMITTAL

 OF PRIORITY DOCUMENT

 mw

(PCT Administrative Instructions, Section 411)

To:

GIDDINGS, Peter, John

 GlaxoSmithKline

 Corporate Intellectual Property

 CN925.1

 980 Great West Road

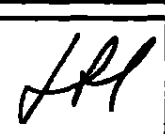
 Brentford, Middlesex TW8 9GS

 United Kingdom

Date of mailing (day/month/year) 17 April 2003 (17.04.03)	
Applicant's or agent's file reference LLK/P32984	IMPORTANT NOTIFICATION
International application No. PCT/GB03/00594	International filing date (day/month/year) 12 February 2003 (12.02.03)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 12 February 2002 (12.02.02)
Applicant GLAXO GROUP LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
12 Febr 2002 (12.02.02)	0203296.9 ✓	GB	20 Marc 2003 (20.03.03)
12 Febr 2002 (12.02.02)	0203297.7 ✓	GB	20 Marc 2003 (20.03.03)
12 Febr 2002 (12.02.02)	0203298.5 ✓	GB	20 Marc 2003 (20.03.03)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.88.85	Authorized officer Luis HIGUERA  Telephone No. (41-22) 338 8164
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Form PCT/IB/304 (July 1998)

006682232

PATENT COOPERATION TREATY

40065

From the INTERNATIONAL BUREAU

13 OCT 2003
 BCT
 INFORMATION CONCERNING ELECTED
 OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 81.3)

To:

THOMPSON, Clive, Beresford
 GlaxoSmithKline, CIP (CN925.1)
 980 Great West Road
 Brentford
 Middlesex TW8 9GS
 United Kingdom

GlaxoSmithKline
 Corporate IP

14 OCT 2003

Received NFSP

Date of mailing (day/month/year) 02 October 2003 (02.10.03)		
Applicant's or agent's file reference LLK/P32984		IMPORTANT INFORMATION
International application No. PCT/GB03/00594	International filing date (day/month/year) 12 February 2003 (12.02.03)	Priority date (day/month/year) 12 February 2002 (12.02.02)
Applicant GLAXO GROUP LIMITED et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI,
 SK, TR
 National : BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW
 EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC,
 EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
 MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN,
 YU, ZA, ZM, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 38(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.85	Authorized officer: Evelyne HUCHON Telephone No. (41-22) 338 9010
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Form PCT/IB/332 (September 1997)

6889652

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION Applicant's or agent's file reference LLK/P32884	
International application No. PCT/GB03/00594	International filing date (day/month/year) 12 February 2003 (12.02.03) (Earliest) Priority date (day/month/year) 12 February 2002 (12.02.02)
Title of invention ORAL DOSAGE FORM FOR CONTROLLED DRUG RELEASE	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Glaxo Group Limited Glaxo Wellcome House Berkeley Avenue, Greenford Middlesex, UB6 0NN United Kingdom	
Telephone No. 020 8047 5000	
Facsimile No. 020 8047 6894	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MARTINI, Luigi GlaxoSmithKline New Frontiers Science Park South, Third Avenue, Harlow, Essex, CM19 5AW United Kingdom	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) RE, Vincenzo GlaxoSmithKline New Frontiers Science Park South Third Avenue, Harlow, Essex, CM19 5AW United Kingdom	
State (that is, country) of nationality: GB	State (that is, country) of residence: GB
☒ Further applicants are indicated on a continuation sheet.	

Sheet No. 2.

International application No.
PCT/GB03/00594

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LI, Chi, Leung
GlaxoSmithKline
New Frontiers Science Park South
Third Avenue, Harlow,
Essex, CM19 5AW
United Kingdom

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

WILLY, Helen, Anne
GlaxoSmithKline
New Frontiers Science Park South
Third Avenue, Harlow,
Essex, CM19 5AW
United Kingdom

State (that is, country) of nationality:
GB

State (that is, country) of residence:
GB

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 3

International application No.
PCT/GB03/00594

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)</i> THOMPSON, Clive Beresford GlaxoSmithKline, CIP (CN925.1) 980 Great West Road, Brentford Middlesex, TW8 9GS United Kingdom	Telephone No. 020 8047 4478
	Facsimile No. 020 8047 8894
	Teleprinter No.
	Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. ☒ The applicant wishes the international preliminary examination to start on the basis of:
☒ the international application as originally filed
the description ☐ as originally filed ☐ as amended under Article 34
the claims ☐ as originally filed ☐ as amended under Article 19 (together with any accompanying statement) ☐ as amended under Article 34
the drawings ☐ as originally filed ☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: **ENGLISH**

☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*
excluding the following States which the applicant wishes not to elect:

Sheet No. .4.

International application No.
PCT/GB03/00594

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

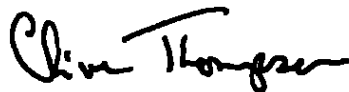
received	not received
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|---|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listings in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ tables in computer readable form related to sequence listings |
| 4. ☒ copy of general power of attorney; reference number, if any: | 8. ☐ other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).


THOMPSON, Clive Beresford
Agent for the Applicants

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60:1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.☐ The applicant has been informed accordingly.4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

Corrected Version / Version corrigée

From the INTERNATIONAL BUREAU

-41101179

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:		GlaxoSmithKline Corporate IP Received BRENTFORD 29 SEP 2003 ATTY IPM ATTY CHANCELLER
GIDDINGS, Peter, John GlaxoSmithKline Corporate Intellectual Property 980 Great West Road Brentford, Middlesex TW8 9QS ROYAUME-UNI		
Date of mailing (day/month/year) 21 August 2003 (21.08.03)		IMPORTANT NOTICE 2003-135 16-11-2003
Applicant's or agent's file reference LLK/P32984		
International application No. PCT/GB03/00594	International filing date (day/month/year) 12 February 2003 (12.02.03)	Priority date (day/month/year) 12 February 2002 (12.02.02)
Applicant GLAXO GROUP LIMITED		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above or the date of mailing of this notice:

AU, AZ, BY, CH, CN, CO, DE, DZ, HU, JP, KG, KP, KR, MD, MK, MZ, RU, TM, US

In accordance with Rule 47.1(c), third sentence, these Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BZ, CA, CR, CU, CZ, DK, DM, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MG, MN, MW, MX, NO, NZ, OA, OM, PH, PL, PT, RO, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

The communication will be made to these Offices only upon their request. Furthermore, these Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-h)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 21 August 2003 (21.08.03) under No. 03/066195

4. **TIME LIMITS** for filing a demand for international preliminary examination and for entry into the national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19936, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limits), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

It is the applicant's sole responsibility to monitor all these time limits.

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Judith Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

Form PCT/IB/308 (April 2002)

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
GLAXOSMITHKLINE
 Corporate Intellectual Property
 Attn. Giddings, Peter John
 980 Great West Road
 (CN925.1)
 Brentford, Middlesex TW8
 UNITED KINGDOM

GlaxoSmithKline Corporate IP	
Received by J. F. RENTFORD	
23 JUN 2003	
ATT. LLK	MIN. MW
IPR. N/A	ON. UPD. ED. ON:
ATTY CHECKED/FILE	

NOTIFICATION OF TRANSMITTAL OF
 THE INTERNATIONAL SEARCH REPORT
 OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
 (day/month/year)

25/06/2003

Applicant's or agent's file reference

LLK/P32984

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/GB 03/00594

International filing date

(day/month/year)

12/02/2003

Applicant

GLAXO GROUP LIMITED

1. ☒ The applicant is hereby notified that the International Search Report has been established and is 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 48).

When? The time limit for filing such amendments is normally 2 months from the date of transmission of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

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 is 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. Further action(s): The applicant is reminded of the following:

Shortly after 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.

Within 19 months from the priority date, 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).

Within 30 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
 NL-2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 apo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Petronella Vaassen-Elsackers

These Notes are intended to give the basic instructions concerning the filing of amendments under article 18. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the international Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 18 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 48.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/ may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequences with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/selected Office, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/selected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference LLK/P32984	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/GB 03/00594	International filing date (day/month/year) 12/02/2003	(Earliest) Priority Date (day/month/year) 12/02/2002
Applicant GLAXO GROUP LIMITED		

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 4 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, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

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:

ORAL DOSAGE FORM FOR CONTROLLED DRUG RELEASE

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(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/00594

J111175

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/44

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)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 01925 A (FORUM CHEMICALS LIMITED) 8 March 1990 (1990-03-08) page 1, line 1 - line 6 page 17, line 2 - line 12 & US 5 004 614 A 2 Apr11 1991 (1991-04-02)	1-13
P, X	WO 02 38131 A (SMITHKLINE BEECHAM P.L.C.) 16 May 2002 (2002-05-16)	12
P, A	page 1, line 1 -page 6, line 15 page 3, line 27 - line 33	1-11, 13
A	GB 2 150 830 A (ALZA CORPORATION) 10 July 1985 (1985-07-10) page 4, column 2, line 75 -column 2, line 118 claims 1,6,8	1-13

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* 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 document 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.

A document member of the same patent family

Date of the actual completion of the international search

16 June 2003

Date of mailing of the international search report

25/06/2003

Name and mailing address of the ISA

European Patent Office, P.O. 6816 Patentkan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Te. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/00594

1176

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 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:

Although claim 13 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 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 an additional fee, this Authority did not invite payment of any additional fee.
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.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/00594

000077

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9001925	A	08-03-1990	AT 110262 T AU 4218489 A CA 1339079 A1 DE 68917677 D1 DE 68917677 T2 EP 0365123 A1 ES 2058543 T3 WO 9001925 A1 GB 2222948 A ,B IE 63764 B1 US 5004614 A	15-09-1994 23-03-1990 29-07-1997 29-09-1994 22-12-1994 25-04-1990 01-11-1994 08-03-1990 28-03-1990 14-06-1995 02-04-1991
WO 0238131	A	16-05-2002	AU 1828002 A WO 0238131 A2	21-05-2002 16-05-2002
GB 2150830	A	10-07-1985	AU 566109 B2 AU 2235483 A CA 1231283 A1 CH 659584 A5 DE 3400496 A1 FR 2560044 A1 JP 1894450 C JP 6023090 B JP 60174713 A	08-10-1987 20-06-1985 12-01-1988 13-02-1987 18-07-1985 30-08-1985 26-12-1994 30-03-1994 09-09-1985

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCION (X)	MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.		(X)	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		(X)	(X)
- Descripción de la invención.		(X)	(X)
- Dibujos de ser estos pertinentes.		()	()
- Comprobante de Pago de las tasas establecidas. (X)		()	()
COMPLETA ()	INCOMPLETA ()		
DISEÑO INDUSTRIAL ()			
- Indicación de que se solicita el registro de Diseño Industrial		()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.		()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.		()	()
- Comprobante de pago de las tasas establecidas		()	()
COMPLETA ()	INCOMPLETA ()		
ESQUEMA DE TRAZADO ()			
- Indicación de que solicita el registro de un Esquema de trazado.		()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.		()	()
- Representación gráfica del esquema de trazado		()	()
- Comprobante de pago de las tasas establecidas.		()	()
COMPLETA ()	INCOMPLETA ()		

Firma Responsable:

Alcudia M Nueva

Fecha: Agosto 9 de 2004.

2020
Bogotá, D.C.,

Doctor:
ALVARO CORREA ORDOÑEZ
Apoderado
GLAXO GROUP LIMITED

Oficio N° 00443

ASUNTO:	Radicación N°	04-77244
	Solicitud Internacional	PCT/GB2003/00594
	Fecha inicio fase nacional	12/09/2004
	Trámite	011
	Evento	379
	Actuación	416
	Folios	001

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:

- 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. (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.
- 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).

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.

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.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento, fue notificado por fijación en lista de fecha, 10 SET 2004

202047