

REYES & REYES

A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMEF

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-097262- -00004-0000

Fecha: 2008-01-29 10:06:10 Dep. 2020 NUECREACIONE
Vía: 11 PATENTEYII Eve: 378 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 42

REF: EXPEDIENTE 05-097-262

TÍTULO SOLICITADO: "PROCESO PARA LA PREPARACION DE UN POLIMORFO DE MALEATO DE ROSIGLITAZONA"

PUBLICACIÓN: Gaceta 573 de 28 de febrero de 2007

PRIORIDAD: GB 0307259.2 DE MARZO 28 DE 2003

SOLICITANTE: GLAXO GROUP LIMITED.

APODERADO: CARLOS REINALDO OLARTE GARCIA.

TRÁMITE: REMISIÓN DE INFORMACIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de la firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del C.S.J, obrando en nombre y representación de **TECNOQUÍMICAS S.A.**, sociedad comercial constituida y vigente de acuerdo con las leyes de la República de Colombia, con domicilio y sede principal en Cali, de manera respetuosa, y con el propósito de coadyuvar en la decisión que sobre la solicitud de patente de la referencia deberá adoptarse próximamente, por este escrito me permito remitir información fundamentada que demuestra que la solicitud en mención **no cumple los requisitos de novedad y nivel inventivo** exigidos por la Decisión 486 de 2000, y que por ello debería el Despacho abstenerse de concederle el privilegio de patente solicitado.

Además de la defensa del orden jurídico vigente en materia de propiedad industrial, el presente escrito se fundamenta en la necesidad de evitar que la concesión de la solicitud vulnere la libre competencia, y restrinja el mercado farmacéutico en perjuicio de los consumidores colombianos.

I. INCUMPLIMIENTO DE REQUISITOS DE PATENTABILIDAD

- **El polimorfismo es una propiedad inherente a todas las moléculas y su reporte es un simple descubrimiento**

Frente a la pretensión de obtener privilegio sobre "un polimorfo de maleato de rosiglitazona" es importante resaltar que existen en la naturaleza infinidad de compuestos orgánicos capaces de adoptar más de una forma cristalina, de igual manera, es necesario recordar que los sólidos pueden existir, de acuerdo con su estructura u ordenamiento interno, en forma cristalina o amorfa, sin que ello signifique que se esté frente a un compuesto o sustancia química diferente, es decir que el Compuesto Químico o Principio Activo, con independencia de la estructura interna que adopte – amorfa o cristalina – sigue siendo el mismo¹.

Es bien sabido que un compuesto cristalino puede cristalizar de diversas formas dependiendo de las condiciones en que cristalice, siendo las más comunes el tipo y/o cantidad de solvente y la temperatura. La publicación "Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates²", revela cerca de 600 casos de polimorfismo en principios farmacéuticos activos y en sustancias carentes de acción farmacológica como son los excipientes; esto nos permite demostrar que el hecho de encontrarnos ahora frente a una modificación cristalina de maleato de rosiglitazona no supone despliegue inventivo, pues se trata simplemente del descubrimiento de la propiedad de una materia conocida³.

- Por si el anterior principio no fuese más que suficiente para dar con la negación de la solicitud de la referencia, es del caso llamar la atención a la materia expuesta en la publicación internacional PCT/WO02/26737 del 4 de abril de 2002 y titulada "NOVEL POLYMORPHIC FORMS OF 5-[4-[2-[M-METHYL-N-(2-PYRIDIL)AMINO]ETHOXY]BENCIL]THIAZOLIDINE-2,4-DIONE MALEATE AND PROCESS FOR THEIR PREPARATION", la cual revela

¹ "Tecnología Farmacéutica Volumen I", José Luis Vila Jato. Editorial Síntesis S.A., Madrid. Páginas 44-50.

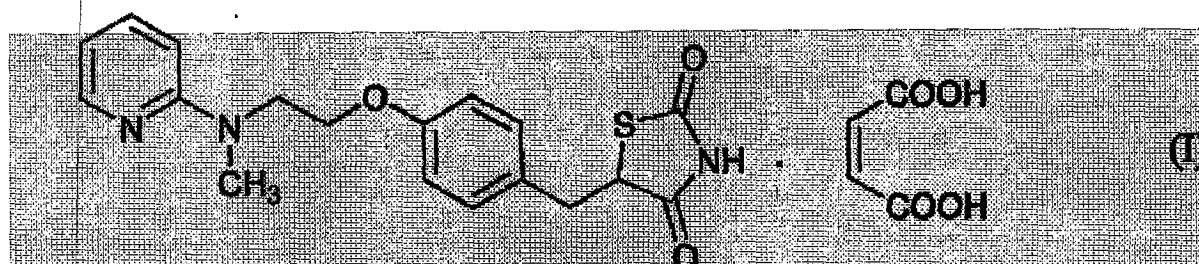
² Giron, D., Thermochemical acta 248-1-59, Elsevier Science B.V., 1995. Páginas 3 a 11.

³ "If a man finds out a new property of a known material or article, that is mere discovery and unpatentable. To find a substance freely occurring in nature is also mere discovery and therefore unpatentable. Guidelines for examination in the European Patent Office.- EPO Pub. 1999, Parte C, capítulo IV, página 36.

3 100

(57) Abstract: This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic form or their mixture and a pharmaceutically acceptable carrier. The polymorphic forms of the present invention are more active, as antidiabetic agent, than the hitherto known 5-[4-[2-[N-(2-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate.

(...)



The present invention also relates to a process for the preparation of various polymorphic/pseudopolymorphic 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula (I) shown below. The

polymorphic forms prepared by the process of the present invention are more active, as an antidiabetic agent.

(...)

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in ethanol,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clear solution and cooling to room temperature over a period of 18 h,
- (iv) isolating the Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

(...)

Este documento permite observar tanto la existencia de polimorfos de Rosiglitazona Maleato como la obtención de los mismos a través de procesos de preparación en donde se hace uso de solventes orgánicos, inclusive etanol, que es uno de los solventes mencionados en la solicitud colombiana en trámite, específicamente en sus reivindicaciones 11 y 13.

El proceso de esta anterioridad básicamente consiste en la preparación de un determinado polimorfo de Rosiglitazona Maleato mediante **“métodos conocidos”** y disolviendo en Etanol, Acetona, metanol, 1,4-dioxano (va a dar uno u otro polimorfo); luego se calienta la solución en un baño de vapor hasta que el sólido esté completamente disuelto; se filtra la solución clara y se enfría a temperatura ambiente por un periodo de 18 horas y se aísla el polimorfo respectivo de Rosiglitazona Maleato formado; si tenemos en cuenta lo anterior con lo revelado en la solicitud colombiana en trámite, vemos que en general, a Rosiglitazona Maleato se le adiciona un solvente (se menciona anisol, isopropilacetato, dicloroetano, n-butanol, dietilacetato, tolueno, propan2-o, entre otros), se calienta por un tiempo determinado, se filtra, se enfría y se obtiene el polimorfo deseado, lo que en consecuencia muestra gran similitud en los procesos descritos, de cuya aplicación se obtienen polimorfos de Rosiglitazona Maleato, conocidos y pertenecientes al estado del arte.

- En el mismo sentido, el documento PCT/WO00/64896 publicado el 2 de noviembre de 2000 y titulado “POLYMORPH OF 5-[4-[2(2-(N-METHYL-N-(2-PYRIDYL(AMINO)ETHOXY]BENZYL]THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT” revela una forma polimórfica de la sal del ácido 5-[4-[2-[N-metil-N-(2-piridil)amino]etoxi]bencil]tiazolidina-2,4-diona maléico caracterizado por i) Espectro IR, ii) espectro de Raman, iii) Espectro de resonancia magnética nuclear C13 en estado sólido, y/o iv) Difracción de polvo de rayos X, su proceso de obtención y composiciones farmacéuticas que lo contienen.

En cuanto al proceso, tenemos que:

WO 00/00/64896

In an alternative process a solution of Compound (I) in denatured ethanol at an elevated temperature, for example 50°C, is seeded with crystals of the Polymorph then cooled, preferably to a temperature in the range of from 20-25°C, so as to provide the Polymorph, after which time the Polymorph is recovered from the denatured ethanol. The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60°C.

CO 05-097-262 (en trámite)

Conveniently this process is carried out by heating the solution of rosiglitazone maleate in denatured ethanol to a temperature of less than 70°C eg 68-69°, adjusting the temperature of the filtrate to approximately 60°C cooling with stirring, then adding the seed material when the solution temperature is approximately 50° and then continuing the cooling to a temperature of less than 25°C and isolating the Compound 1 by filtration.

Como puede apreciarse, los dos procesos emplean Rosiglitazona Maleato en etanol desnaturalizado a una temperatura de 50°C, cuando se encuentra en esta temperatura se adiciona o se siembra el material y se enfría hasta temperatura de 25°C y luego se aísla o se recupera el compuesto final, lo que en consecuencia demuestra que uno y otro proceso son muy similares, razón por la cual la solicitud colombiana en trámite no cumple con los requisitos de patentabilidad contenidos en la Decisión 486 de 2000.

En el mismo sentido, el ejemplo 3 de la WO 00/64896 y el ejemplo 23 de la solicitud colombiana en trámite también son muy similares, en tanto emplean las mismas condiciones en presencia de etanol desnaturalizado o IMS (Industrial Methylated Spirit):

Example 3: Conversion of Polymorph to Compound (I)

A mixture of Polymorph (10.0 g) in denatured ethanol (90 ml) was heated under nitrogen to give a clear solution. The clear solution was stirred at 62°C for 30 min then filtered hot to a vessel preheated to 55°C. The filter was washed with hot denatured ethanol (10 ml). The temperature of the filtrate was adjusted to 60°C before cooling, with stirring, at about 1deg/min. The cooling mixture was seeded at 52°C with Compound (I) (0.4 g) and cooling at 1°C/min with stirring was continued. The resultant slurry was stirred at ambient temperature for 1 h and the solid was isolated by filtration, washed with denatured ethanol and dried *in vacuo* at 50°C to give 8.4 g (84%) of Compound (I).

WO 00/64896

Example 23

A mixture of rosiglitazone (7.5 g) and maleic acid (2.55 g) was heated to 70°C in industrial methylated spirit (75 mL) under nitrogen. After 30 minutes the clear solution was transferred to a pre-heated vessel via an in-line filter under nitrogen pressure. The solution was reheated to 70°C with stirring and then cooled to 55°C before being seeded with Compound 1 (0.3 g, prepared as in Example 4B). The mixture was cooled to 20° and stirred for 1 hour. The product was filtered, washed with industrial methylated spirit and dried to give Compound 1 (8.66 g, 85%)

CO 05-097-262

La anterioridad citada en sus ejemplos 2 y 3 hace uso de solventes como acetona y etanol desnaturalizado que son mencionados en el capítulo descriptivo de la solicitud colombiana en trámite, específicamente en los ejemplos 20 y 21, y reivindicaciones 11 y 13; de la misma manera, algunas condiciones de cristalización tales como el uso de atmósfera de nitrógeno y temperaturas menores a 70°C durante dichos procesos de obtención de los polimorfos, también se señalan en dicha anterioridad tal y como se menciona en el capítulo descriptivo de la solicitud colombiana en trámite (ejemplo 23).

- La patente europea EP 1277753 publicada el 22 de Enero de 2003 y titulada "THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC" revela:

[0017] In a further aspect, the invention provides a process for converting Polymorph to Compound (I), wherein a solution of Polymorph in a suitable solvent, such as acetone or ethanol, is seeded with Compound (I); preferably the reaction is carried out in an inert atmosphere, such as nitrogen. Generally, the solution of Polymorph is obtained by dissolving Polymorph at an elevated temperature in the solvent, such as acetone or ethanol.

(...)

7 12A

Example 1: Preparation of the Polymorph.

[0046] A mixture of maleic acid (2.10 g) and 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (6.0 g) were heated to 70°C in denatured ethanol (60 ml, 5% v/v methanol) until complete dissolution was obtained. The resultant solution was filtered, re-heated to 67.5°C, and then cooled to 20-25°C. The resulting crystalline product was filtered off, washed with denatured ethanol (10 ml) and dried at 50°C *in vacuo* to give the Polymorph (6.61 g, 83%).

Example 2: Conversion of Polymorph to Compound (I)

[0047] Polymorph (10.0 g) was added to denatured ethanol (90 ml) under nitrogen. The resulting mixture was stirred and heated to 68°C, and held at this temperature for 30 min. The solution was hot filtered to a preheated vessel (56°C) and the filter washed with hot denatured ethanol (10 ml). The temperature of the filtrate was adjusted to 60°C and then cooled with stirring. At 55°C the solution was seeded with Compound (I) (0.4 g) and cooling, with stirring, continued. The resulting slurry was stirred at ambient temperature for 1 h, and the solid isolated by filtration, washed with denatured ethanol and dried at 50°C *in vacuo* to give 8.4 g (84%) Compound (I).

Example 3: Conversion of Polymorph to Compound (I)

[0048] Polymorph (5.0 g) was added to acetone (170 ml) and the mixture was stirred and heated to reflux temperature. After complete dissolution, the solution was heated at reflux for 30 min, then filtered. The filtered solution was concentrated by distillation at atmospheric pressure (120 ml of distillate was collected). The remaining solution was stirred and cooled at about 1°C/min and at 50°C seeded with Compound (I) (0.2 g). Cooling was continued at 1°C/min, and when the slurry reached 20°C stirring was continued for 1 h. The solid was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 4.2 g (84%) of Compound (I).

(...)

Además reivindica:

9. A process for preparing a Polymorph according to claim 1, characterised in that a solution of Compound (I) in denatured ethanol at an elevated temperature is cooled so as to provide crystallisation of the Polymorph after which the Polymorph is recovered from the denatured ethanol.

Este documento señala claramente que en la obtención del Polimorfo de Rosiglitazona Maleato se emplean solventes como acetona (que se mencionan en el capítulo descriptivo de la solicitud colombiana en trámite, específicamente en los ejemplos 20 y 21), etanol desnaturalizado (incluido en las reivindicaciones 11 y 13 de la solicitud colombiana en trámite) y condiciones de cristalización tales como el uso de atmósfera de nitrógeno (ejemplo 23 de la solicitud colombiana en trámite) en la obtención de polimorfos de maleato de rosiglitazona. Así mismo se hace mención de temperaturas menores a 70°C durante dichos procesos de obtención, tal y como se menciona en el capítulo descriptivo de la solicitud colombiana en trámite.

- De nuevo la patente europea EP 1284268 publicada el 19 de Febrero de 2003 y titulada "THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC"

8/101

revela, al igual que los documentos señalados a lo largo de este escrito, una forma polimórfica de la sal del ácido 5-[4-[2-[N-metil-N-(2-piridil)amino]etoxi] bencil] tiazolidina-2,4-diona maléico caracterizado por i) Espectro IR, ii) espectro de Raman, iii) Espectro de resonancia magnética nuclear C13 en estado sólido, y/o iv) Difracción de polvo de rayos X, su proceso de obtención y composiciones farmacéuticas que lo contienen.

El proceso consiste en:

[0015] The invention also provides a process for preparing the Polymorph, characterised in that a slurry of Compound (I) in aqueous ethanol containing up to about 2.5% w/v water, preferably aqueous denatured ethanol containing up to about 2.5% w/v water, for example 2.5% w/v water, is heated, suitably to a temperature in the range of from 35°C and 60°C, such as 40°C to 50°C, for example to 45°C, for an extended period of time, for example 65 hours, after which time the Polymorph is recovered from the denatured ethanol. Optionally, the reaction mixture is seeded with the Polymorph.

[0016] In a further process of the invention, Compound (I) is admixed with denatured ethanol, heated to an elevated temperature, preferably a temperature in the range of from 35°C and 60°C, such as 40°C to 50°C, for example from 45° to 47°C, over an extended period of time, for example 65 hours, after which time the Polymorph is recovered from the solvent. Optionally, the reaction mixture is seeded with Polymorph.

[0017] In a further process a solution of Compound (I) in denatured ethanol containing up to 2.5% w/v water, for example 0.8 to 2.5% w/v water, at 55°C is seeded with the Polymorph then cooled to a temperature in the range of from 20°C to 25°C to provide the Polymorph. The Polymorph is then recovered from the denatured ethanol.

[0018] The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60°C. In our hands this latter process is also effectively carried out using Compound (I) containing up to 25% w/w of the hydrate disclosed in WO99/31093 mentioned above

[0019] Conveniently the Polymorph is recovered from the reaction solvent, such as denatured ethanol, by filtration and subsequent drying, preferably at an elevated temperature, for example 45°C.

(...)

Además reivindica:

9. A process for preparing a Polymorph according to claim 1, characterised in that:

(a) a slurry of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)" or the "Original Polymorph") in aqueous ethanol containing up to about 2.5% w/v water, is heated for an extended period of time; after which time the Polymorph is recovered from the denatured ethanol; or

(b) Compound (I) is admixed with denatured ethanol, heated to an elevated temperature, over an extended period of time, after which time the Polymorph is recovered from the solvent; or

(c) Compound (I) in denatured ethanol containing up to 2.5% w/v water at 55°C is seeded with the Polymorph then cooled to a temperature in the range of from 20°C to 25°C to provide the Polymorph;

Claramente se evidencia que los procesos aquí revelados como los de la solicitud colombiana son muy .

Ahora bien, y para terminar es importante mencionar que, si la caracterización de la presente solicitud está dada por el uso de solventes específicos o solventes con una constante dieléctrica determinada, es claro que las anterioridades mencionadas ya revelaban y empleaban en sus procesos solventes como la acetona, metanol o etanol, los cuales, y según literatura científica, son solventes que tiene una constante dieléctrica de 20,7 para la acetona: 32,6 para el metanol y 24,3 para el etanol; si bien es cierto estos valores son superiores a 21 (en el caso del metanol y el etanol), es del caso resaltar que existen solventes con constante dieléctrica inferior a 21 como por ejemplo⁴:

Anisol: 4.33	Acetato de etilo: 6.02
Tetrahidrofurano: 7.52	Diclorometano: 8.93
1-butanol: 17.8	1-propanol: 20.1
Metil etil cetona: 18.5	Hexano: 2.02
Eter dietílico: 4.3	Cloroformo: 4.8
Tetracloruro de Carbono: 2.24	Cloruro de Metileno: 9.08

Como vemos, varios de los solventes mencionados en el párrafo anterior son empleados en la solicitud colombiana en trámite, lo que deja ver claramente que estos solventes y su constante dieléctrica es conocida en el estado del arte y que dada su baja constante dieléctrica (generalmente para los solventes no polares) permiten que los iones de cargas opuestas se atraigan tan fuertemente como para formar una sal; si por el contrario, las fuerzas son débiles como ocurre con un solvente con constante dieléctrica alta, permite que cantidades significativas de iones permanezcan separadas, lo que podría explicar de alguna manera el porque se usa este tipo de solventes, sin que definitivamente, nos encontremos frente a un avance frente al arte anterior.

En conclusión, siendo las condiciones tales como temperatura y solvente, características esenciales para la obtención de una forma polimorfa definida, y siendo estas mismas condiciones incluidas en anterioridades donde también se busca la obtención de diversos polimorfos de maleato de rosiglitazona, resulta obvia aplicación de las mismas al proceso de obtención de las formas polimórficas de la solicitud colombiana en trámite, con lo que el solicitante no puede argumentar el nivel inventivo requerido e indispensable para una patente de invención.

⁴ <http://www.ugr.es/~quiorred/lab/ctes/ctes.htm>

10 57

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

III. PRUEBAS

Ruego que se tengan como tales las siguientes, sin perjuicio de aquellas que el Despacho considere oficiosamente, las siguientes:

- La publicación internacional WO 02/26737 publicada el 04 de Abril de 2002 y titulada "NOVEL POLYMORPHIC FORMS OF 5-[4-[2-[M-METHYL-N-(2-PYRIDIL)AMINO]ETHOXY]BENCIL]THIAZOLIDINE-2,4-DIONE MALEATE AND PROCESS FOR THEIR PREPARATION" paginas 1, 7 y capitulo reivindicatorio.
- La publicación internacional WO 00 /64896 publicada el 02 de Noviembre de 2000 y titulada "POLYMORPH OF 5-[4-[2(2-(N-METHYL-N-(2-PYRIDYL(AMINO) ETHOXY] BENZYL]THIAZOLIDINE-2,4-DIONE, MALEIC ACID SALT" paginas 2, 7 y capitulo reivindicatorio.
- La patente europea EP 1277753 publicada el 22 de Enero de 2003 y titulada "THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC" paginas 2, 4 y capitulo reivindicatorio.
- La patente europea EP 1284268 publicada el 19 de Febrero de 2003 y titulada "THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC" paginas 2, 4 y capitulo reivindicatorio.
- Tecnología Farmacéutica Volumen I", José Luis Vila Jato. Editorial Síntesis S.A., Madrid. Páginas 44-50.
- Giron, D., Thermochemica acta 248-1-59, Elsevier Science B.V., 1995. Páginas 3 a 11.

IV. NOTIFICACIONES

Mi representada y el suscrito las recibiremos en la secretaría de su Despacho, o en mi oficina de abogado, ubicada en la Carrera 17 No. 88-23, Oficina 205 de Bogotá, Fax (1) 621.25.42.

11/108

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR

C.C. No. 79.152.473 (Usaquén)

T.P. No. 44055 del C. S. J.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 April 2002 (04.04.2002)

PCT

(10) International Publication Number
WO 02/26737 A1

(51) International Patent Classification⁷: **C07D 417/12**,
277/34, A61K 31/425, A61P 3/10, 9/12

(21) International Application Number: **PCT/US01/29896**

(22) International Filing Date:
25 September 2001 (25.09.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
805/MAS/00 26 September 2000 (26.09.2000) IN

(71) Applicant (for all designated States except GD, US):
REDDY'S RESEARCH FOUNDATION [IN/IN];
7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh
(IN).

(71) Applicant (for GD only): **CORD, Janet, I.** [US/US]; 26
West 61st Street, New York, NY 10023 (US).

(72) Inventors; and

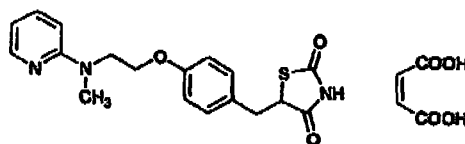
(75) Inventors/Applicants (for US only): **CHEBIYYAM, Prabhakar** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN). **MAMILLAPALLI, Ramabhadra, Sarma** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN). **KRISHNAMURTHI, Vyas** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN). **SEELLA, Vishnuvardhan, Reddy** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN). **GADDAM, Om, Reddy** [IN/IN]; 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh (IN).

(74) Agents: **CORD, Janet, I. et al.; Ladas & Parry**, 26 West 61st Street, New York, NY 10023 (US).

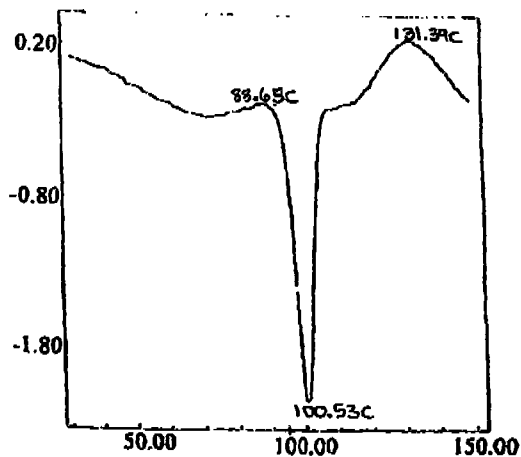
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI,

[Continued on next page]

(54) Title: **NOVEL POLYMORPHIC FORMS OF 5-[4-[2-[N-METHYL-N-(2-PYRIDYL)AMINO]ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE MALEATE AND PROCESS FOR THEIR PREPARATION**



(i)



(57) Abstract: This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic form or their mixture and a pharmaceutically acceptable carrier. The polymorphic forms of the present invention are more active, as antidiabetic agent, than the hitherto known 5-[4-[2-[N-(2-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate.

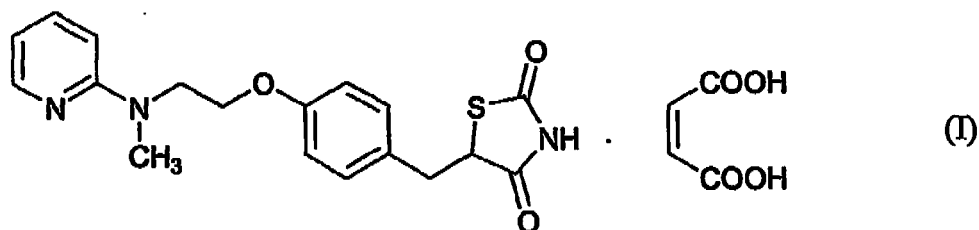
WO 02/26737 A1

- 1 -

NOVEL POLYMORPHIC FORMS OF 5-[4-[2-[N-METHYL-N-(2-PYRIDYL)AMINO]ETHOXY]BENZYL] THIAZOLIDINE-2,4-DIONE MALEATE
AND PROCESS FOR THEIR PREPARATION

Field of the Invention

5 This invention relates to novel polymorphic/pseudopolymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate and its stereo- isomers having formula (I). The invention also relates to a pharmaceutical composition comprising the novel polymorphic form or their mixture and a pharmaceutically acceptable carrier. The polymorphic forms of the present invention are
10 more active, as antidiabetic agent, than the hitherto known 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl] thiazolidine-2,4-dione maleate.



The present invention also relates to a process for the preparation of various polymorphic/pseudopolymorphic 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl]thiazolidine-2,4-dione maleate, having the formula (I) shown below. The
15 polymorphic forms prepared by the process of the present invention are more active, as an antidiabetic agent.

The polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of formula (I) defined above of the present invention
20 reduce blood glucose and has beneficial effect on coronary heart disease and atherosclerosis.

Out of the many drugs available for the treatment of diabetic ailments, the thiazolidine dione derivatives are very prominent and are considered as much superior effective constituents compared to the sulphonyl ureas. 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, one such thiazolidinedione
25 which exhibited euglycemic effect, was reported in the year 1988 by Beecham group England (EP 0306228A1) and created interest in the field, ever since.

The novel polymorphic forms of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy] benzyl]thiazolidine-2,4-dione maleate, of formula (I) defined above of the present

- 7 -

XRD (2 θ): 4.60, 8.46, 9.24, 14.98, 15.86, 17.02, 18.60, 21.92, 23.50, 25.00, 25.44, 26.00, 26.38, 28.34, 33.90 (Fig. 7).

IR : 3429 (m), 2949 (m), 2738 (m), 1747 (w), 1704 (s), 1641 (m), 1617 (m), 1513 (s), 1464 (m), 1352 (m), 1244 (s), 1178 (s), 1069 (m), 862 (w), 777 (s), 717 (m), 657 (m), 589 (w) (Fig. 12).

According to yet another feature of the present invention, there is provided a novel polymorphic Form-IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I which is characterized by the following data:

DSC : Endotherm at 125.39°C (on set at 121.03°C) (Fig. 4).

XRD (2 θ): 7.4, 8.8, 9.54, 14.98, 15.32, 15.82, 16.90, 17.70, 18.40, 18.54, 19.08, 19.72, 20.22, 20.48, 21.36, 21.66, 22.18, 22.58, 23.32, 23.96, 24.52, 25.38, 26.48, 27.00, 27.58, 27.94, 28.34, 28.54, 28.84, 29.10, 29.86, 30.02, 30.40, 30.52, 30.84, 31.40, 31.94 (Fig. 8).

IR : 3433 (m), 2930 (m), 1753 (w), 1705 (s), 1642 (w), 1617 (m), 1512 (s), 1467 (w), 1351 (m), 1244 (m), 1162 (m), 1061 (w), 864 (s), 765 (s), 714 (w), 658 (m), 526 (w) (Fig. 13).

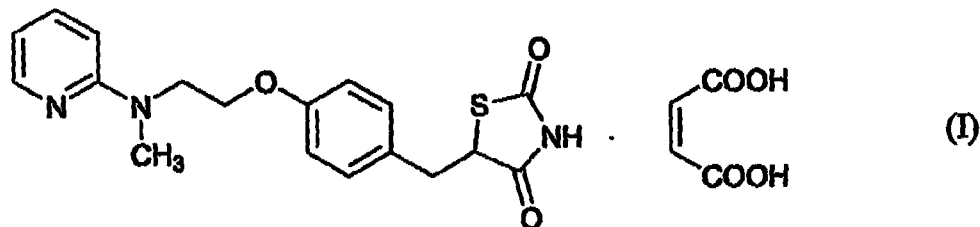
According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of the formula I, having the characteristics described earlier, which comprises:

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in ethanol,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clear solution and cooling to room temperature over a period of 18 h,
- (iv) isolating the Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.

According to another feature of the present invention, there is provided a process for the preparation of novel polymorphic Form-II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, of the formula I, having the characteristics described earlier, which comprises:

- 13 -
CLAIMS

1. A novel polymorphic Form-I of 5-[4-[2-[N-methyl-N-(2-pyridyl) amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I



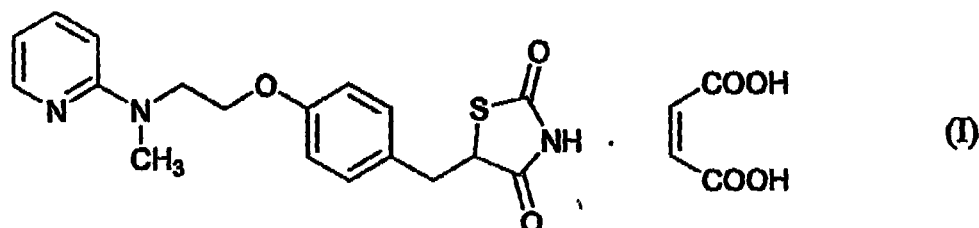
5 which is characterized by the following data:

DSC endotherm at 100.53°C (on set at 88.65°C),

X Ray powder diffraction (2 θ) : 10.90, 14.54, 15.96, 18.46, 18.60, 19.76, 20.72, 21.84, 22.36, 22.46, 23.90, 24.04, 24.72, 25.30, 25.98, 27.44, 29.70,

10 IR (cm⁻¹) : 3435 (m), 2997 (w), 2773 (m), 1750 (m), 1701 (s), 1620 (m), 1510 (m), 1362 (m), 1332 (m), 1237 (s), 1165 (m), 864 (s), 764 (s), 717 (m), 654 (m), 540 (w).

2. A novel polymorphic Form-II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I



which is characterized by the following data:

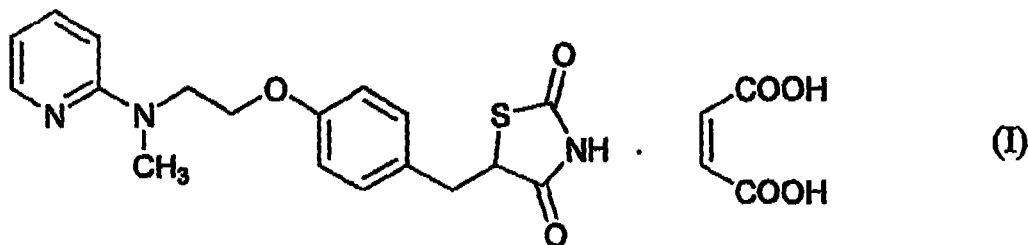
15 DSC : Endotherm at 127.67°C (on set at 123.17°C),

XRD (2 θ): 8.90, 15.40, 18.06, 19.20, 22.30, 23.40, 23.62, 24.80, 25.10, 25.84, 26.72, 27.18, 29.30, 29.54, 29.84, 33.26,

20 IR : 3424 (w), 3040 (w), 2947 (m), 2720 (m), 1751 (m), 1702 (s), 1641 (m), 1618 (m), 1574 (w), 1541 (w), 1412 (w), 1382 (w), 1359 (m), 1326 (m), 1265 (w), 1242 (s), 1213 (w), 1162 (s), 1067 (w), 1031 (w), 865 (s), 773 (s), 713 (s), 667 (m), 576 (w), 539 (m).

3. A novel polymorphic Form-III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate and its stereoisomers having the formula I

- 14 -



which is characterized by the following data:

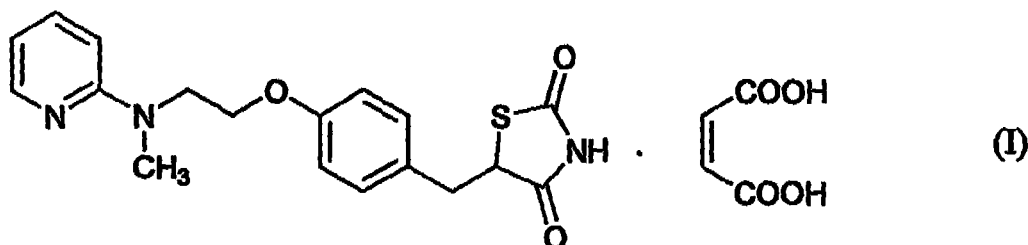
DSC : Endotherm at 126.41°C (on set at 122.06°C),

XRD (2θ): 4.60, 8.46, 9.24, 14.98, 15.86, 17.02, 18.60, 21.92, 23.50, 25.00,

5 25.44, 26.00, 26.38, 28.34, 33.90,

IR : 3429 (m), 2949 (m), 2738 (m), 1747 (w), 1704 (s), 1641 (m), 1617 (m), 1513 (s), 1464 (m), 1352 (m), 1244 (s), 1178 (s), 1069 (m), 862 (w), 777 (s), 717 (m), 657 (m), 589 (w).

4. A novel polymorphic Form-IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, and its stereoisomers having the formula I



which is characterized by the following data:

DSC : Endotherm at 125.39°C (on set at 121.03°C),

15 XRD (2θ): 7.4, 8.8, 9.54, 14.98, 15.32, 15.82, 16.90, 17.70, 18.40, 18.54, 19.08, 19.72, 20.22, 20.48, 21.36, 21.66, 22.18, 22.58, 23.32, 23.96, 24.52, 25.38, 26.48, 27.00, 27.58, 27.94, 28.34, 28.54, 28.84, 29.10, 29.86, 30.02, 30.40, 30.52, 30.84, 31.40, 31.94,

IR : 3433 (m), 2930 (m), 1753 (w), 1705 (s), 1642 (w), 1617 (m), 1512 (s), 1467 (w), 1351 (m), 1244 (m), 1162 (m), 1061 (w), 864 (s), 765 (s), 714 (w), 658 (m), 526 (w).

5. A process for the preparation of novel polymorphic Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises

- (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in ethanol,
 - (ii) heating the solution in a steam bath till the solid completely dissolved,
 - (iii) filtering the clean solution and cooling to room temperature over a period
- 25 of 18 h and

- 15 -

- (iv) isolating the Form I of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.
6. A process for the preparation of novel polymorphic Form II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises:
- 5 (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in acetone,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clean solution and cooling to room temperature over a period of 18 h and
- 10 (iv) isolating the Form II of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.
7. A process for the preparation of novel polymorphic Form III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises:
- 15 (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in methanol,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clean solution and cooling to room temperature over a period of 18 h and
- 20 (iv) isolating the Form III of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.
8. A process for the preparation of novel polymorphic Form IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, which comprises:
- 25 (i) synthesizing 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, employing known methods and dissolving in 1,4-dioxane,
- (ii) heating the solution in a steam bath till the solid completely dissolved,
- (iii) filtering the clean solution and cooling to room temperature over a period of 18 h and
- 30 (iv) isolating the Form IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate formed.
9. A pharmaceutical composition comprising a mixture of any of polymorphic Forms

- 16 -

I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, of the formula (I) and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

10. A pharmaceutical composition as claimed in claim 9, in the form of a tablet, capsule, powder, syrup, solution or suspension.
11. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 to a patient in need thereof.
12. A method according to claim 11, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.
13. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl] thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10.
14. A method of preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed

- 17 -

in claims 9 and 10 in combination / concomitant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.

- 5 15. A method according to claim 14, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders
10 related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma and cancer.
16. A method according to claim 14 for the treatment and / or prophylaxis of disorders
15 related to Syndrome X, which comprises administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 in combination with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to
20 act synergistically together.
17. A method of reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises administering a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a
25 pharmaceutical composition as claimed in claims 9 and 10 in combination / concomitant with HMG CoA reductase inhibitors or fibrates or nicotinic acid or cholestyramine or colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof.
18. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as
30 defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis,

- 18 -

obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

19. Use of a polymorphic Form according to claim 18, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
20. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.
21. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 in combination/ concomitant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism to a patient in need thereof.
22. Use of a polymorphic Form according to claim 21, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive

- 19 -

functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

23. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as
5 defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.
24. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-
10 pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preparing a medicament for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological
15 mechanism.
25. Use of a polymorphic form according to claim 24, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hyper-tension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis,
20 glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
26. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as
25 defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preparing a medicament for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma.
27. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as
30 defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for

- 20 -

preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for preventing or treating hyperlipemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism.

28. Use of a polymorphic form according to claim 27, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

29. Use of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 for preparing a medicament in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL or free fatty acids in the plasma.

30. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising administering an effective amount of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10.

31. A medicine according to claim 30, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy,

- 21 -

nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.

- 5 32. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma comprising an effective amount of a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10.
- 10 33. A medicine for preventing or treating hyperlipidemia, hypercholesteremia, hyperglycemia, osteoporosis, obesity, glucose intolerance, leptin resistance, insulin resistance, or diseases in which insulin resistance is the underlying pathophysiological mechanism comprising a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione maleate, having the
- 15 formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.
34. A medicine according to claim 33, wherein the disease is type II diabetes, impaired glucose tolerance, dyslipidaemia, disorders related to Syndrome X such as
- 20 hypertension, obesity, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders, certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis, retinopathy, nephropathy, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), useful as aldose reductase inhibitors, for improving cognitive
- 25 functions in dementia and treating diabetic complications, osteoporosis, inflammatory bowel diseases, myotonic dystrophy, pancreatitis, arteriosclerosis, xanthoma or cancer.
35. A medicine for reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma, which comprises a polymorphic Form selected from Form I to IV of 5-[4-[2-[N-methyl-N-(2-pyridyl)amino]ethoxy]benzyl]thiazolidine-
- 30 2,4-dione maleate, having the formula I as defined in claims 1-4 or a pharmaceutical composition as claimed in claims 9 and 10 and HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
2 November 2000 (02.11.2000)

PCT

(10) International Publication Number
WO 00/64896 A1

(51) International Patent Classification¹: C07D 417/12,
A61K 31/44, A61P 3/10

Beecham (Cork) Limited, Curraghbinny, Carrigaline,
County Cork (IE).

(21) International Application Number: PCT/GB00/01520

(74) Agent: RUTTER, Keith; SmithKline Beecham, Two New
Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(22) International Filing Date: 19 April 2000 (19.04.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9909473.2 23 April 1999 (23.04.1999) GB
9912196.4 25 May 1999 (25.05.1999) GB

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ,
BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK,
DM, DZ, 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, NO, NZ, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU,
MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (*for all designated States except US*):
SMITHKLINE BEECHAM PLC [GB/GB]; New
Horizons Court, Brentford, Middlesex TW8 9EP (GB).
SMITHKLINE BEECHAM (CORK) LIMITED
[IE/IE]; Curraghbinny, Carrigaline, County Cork (IE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BLACKLER, Paul,
David, James [GB/GB]; SmithKline Beecham Pharma-
ceuticals, Old Powder Mills, Near Leigh, Tonbridge, Kent
TN11 9AN (GB). BROWNE, Christine, Marie [IE/IE];
SmithKline Beecham (Cork) Limited, Curraghbinny,
Carrigaline, County Cork (IE). COAKLEY, Timothy, G.
[IE/IE]; SmithKline Beecham (Cork) Limited, Curragh-
binny, Carrigaline, County Cork (IE). GILES, Robert,
Gordon [GB/GB]; SmithKline Beecham Pharmaceuticals,
Old Powder Mills, Near Leigh, Tonbridge, Kent TN11
9AN (GB). MORRISSEY, Gillian [IE/IE]; SmithKline

Published:

— with international search report

(48) Date of publication of this corrected version:

25 October 2001

(15) Information about Correction:

see PCT Gazette No. 43/2001 of 25 October 2001, Section
II

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

WO 00/64896 A1

(54) Title: POLYMORPH OF 5-[4-[2- (N-METHYL-N-(2-PYRIDYL)AMINO) ETHOXY]BENZYL] THIAZOLI-
DINE-2,4-DIONE, MALEIC ACID SALT

(57) Abstract: A polymorphic form of 5-[4-[2- (N-methyl-N-(2-pyridyl)amino) ethoxy]benzyl] thiazolidine-2, 4-dione, maleic acid salt (the "Polymorph") characterised in that it provides: (i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm⁻¹; and/or (ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm⁻¹; and/or (iii) a solid-state ¹³C nuclear magnetic resonance spectrum containing peaks at 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5, 171.0, 178.7 ppm; and/or (iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

5 The present invention encompasses the Polymorph isolated in pure form or when admixed with other materials, for example the known forms of Compound I (or the "Original Polymorph") or any other material.

Thus in one aspect there is provided the Polymorph in isolated form.

In a further aspect there is provided the Polymorph in pure form.

In yet a further aspect there is provided the Polymorph in crystalline form.

10 The invention also provides a process for preparing the Polymorph, characterised in that Compound (I) is suspended in acetone, preferably under an inert atmosphere such as nitrogen, and stirred at an elevated temperature, preferably reflux temperature, for an extended period of time, for example 17 hours, after which time the Polymorph is isolated from the reaction mixture.

15 In an alternative process a solution of Compound (I) in denatured ethanol at an elevated temperature, for example 50°C, is seeded with crystals of the Polymorph then cooled, preferably to a temperature in the range of from 20-25°C, so as to provide the Polymorph, after which time the Polymorph is recovered from the denatured ethanol. The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of
20 denatured ethanol at an elevated temperature, for example 60°C.

Typically the Polymorph is recovered from the reaction by filtration and subsequent drying, usually at an elevated temperature, for example 50°C.

25 In a further aspect, the invention provides a process for converting Polymorph to Compound (I), wherein a solution of Polymorph in a suitable solvent, such as acetone or ethanol, is seeded with Compound (I). Generally, the solution of Polymorph is obtained by dissolving Polymorph at an elevated temperature in the solvent, such as acetone or ethanol.

30 Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference.

For the avoidance of doubt the term "Compound (I)" as used herein refers to the form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt as disclosed and characterised in International Patent Application, Publication Number WO94/05659.

35 When used herein "denatured ethanol" means ethanol containing small amounts of methanol, usually up to 5% v/v of methanol, such as from 0.9% v/v to 5% v/v of methanol, for example ethanol containing 4%v/v of methanol.

Example 1: Preparation of Polymorph

Compound (I) (8.0 g) was suspended in acetone (80 ml) under nitrogen and the resulting slurry was stirred at reflux for 17.5 h. The mixture was then cooled to ambient and stirred for 30 min. The product was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 6.9 g (86%) of the Polymorph.

Example 2: Conversion of Polymorph to Compound (I)

Polymorph (18.0 g) was added to acetone (450 ml) and the resultant mixture was heated at reflux under nitrogen for 30 min. The hot solution was filtered, and the filtered solution was concentrated by distillation at atmospheric pressure (270 ml of acetone was collected). The concentrated solution was then allowed to cool at about 1°C/min and at 50°C the solution was seeded with Compound (I) (0.09 g). Cooling at about 1°C/min was continued. The resulting slurry was stirred for 1 h at ambient temperature, then the solid was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 15.1 g (84%) of Compound (I).

Example 3: Conversion of Polymorph to Compound (I)

A mixture of Polymorph (10.0 g) in denatured ethanol (90 ml) was heated under nitrogen to give a clear solution. The clear solution was stirred at 62°C for 30 min then filtered hot to a vessel preheated to 55°C. The filter was washed with hot denatured ethanol (10 ml). The temperature of the filtrate was adjusted to 60°C before cooling, with stirring, at about 1 deg/min. The cooling mixture was seeded at 52°C with Compound (I) (0.4 g) and cooling at 1°C/min with stirring was continued. The resultant slurry was stirred at ambient temperature for 1 h and the solid was isolated by filtration, washed with denatured ethanol and dried *in vacuo* at 50°C to give 8.4 g (84%) of Compound (I).

CHARACTERISING DATA: The following characterising data were generated for the polymorph:

A Infrared

The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm⁻¹ resolution. Data were digitised at 1 cm⁻¹ intervals. The spectrum obtained is shown in Figure I. Peak positions are as follows 1763, 1702, 1643, 1623, 1578, 1542, 1515, 1416, 1356, 1334, 1302, 1284, 1261, 1243, 1224, 1201, 1184, 1179, 1147, 1109, 1081, 1055, 1033, 1015, 975, 959, 912, 888, 856, 833, 798, 776, 759, 744, 722, 709, 651, 617, 604, 596, 581, 539, 524 and 505 cm⁻¹.

22
124

CLAIMS

1. A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the Polymorph)
5 characterised in that it provides:
- (i) an infra red spectrum containing peaks at 1763, 912, 856 and 709 cm^{-1} ; and/or
 - (ii) a Raman spectrum containing peaks at 1762, 1284, 912 and 888 cm^{-1} ; and/or
 - (iii) a solid-state ^{13}C nuclear magnetic resonance spectrum containing peaks at
10 111.0, 113.6, 119.8, 129.1, 130.9, 131.8, 134.7, 138.7, 146.5, 152.7, 157.5, 169.5,
171.0, 178.7 ppm; and/or
 - (iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice
spacings at 5.87, 5.30, 4.69, 4.09, 3.88, 3.61, 3.53 and 3.46 Angstroms
- 2.. A Polymorph according to claim 1, which provides an infra red spectrum
15 substantially in accordance with Figure I.
3. A Polymorph according to claim 1 or claim 2, which provides provides a
Raman spectrum substantially in accordance with Figure II.
- 20 4. A Polymorph according to any one of claims 1 to 3, which provides provides a
solid-state ^{13}C nuclear magnetic resonance spectrum substantially in accordance with
Figure III and/or Table I.
5. A Polymorph according to any one of claims 1 to 3, which provides an X-ray
25 powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or
Table II.
6. A Polymorph according to any one of claims 1 to 5, in isolated form.
- 30 7. A Polymorph according to any one of claims 1 to 6, in pure form.
8. A Polymorph according to any one of claims 1 to 7, in crystalline form.
9. A process for preparing a Polymorph according to claim 1, characterised in
35 that either:
- (a) Compound (I) is suspended in acetone and stirred at an elevated temperature
for an extended period of time; or

28
125

(b) Compound (I) in denatured ethanol at an elevated temperature is seeded with crystals of the Polymorph, the reaction mixture is then cooled so as to provide the Polymorph;
after which time the Polymorph is recovered from the denatured ethanol.

5

10. A pharmaceutical composition comprising an effective, non-toxic amount of a Polymorph according to claim 1 and a pharmaceutically acceptable carrier therefor.

11. A Polymorph according to claim 1, for use as an active therapeutic substance.

10

12. A Polymorph according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

15

13. The use of Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

20

14. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph to a human or non-human mammal in need thereof.

29
126

(19)  **Europäisches Patentamt**
European Patent Office
Office européen des brevets



(11) **EP 1 277 753 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
22.01.2003 Bulletin 2003/04

(51) Int Cl.7: **C07D 417/12, A61K 31/427,
A61P 3/10**

(21) Application number: **02080319.3**

(22) Date of filing: **19.04.2000**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**
Designated Extension States:
AL LT LV MK RO SI

- **Giles, Robert Gordon, c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)**
- **Moore, Stephen, c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)**
- **Sasse, Michael, John c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)**

(30) Priority: **23.04.1999 GB 9909471
25.05.1999 GB 9912195**

(74) Representative: **Rutter, Keith et al
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.1)
980 Great West Road
Brentford, Middlesex TW8 9GS (GB)**

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
00922793.5 / 1 175 418

(71) Applicant: **SmithKline Beecham plc
Brentford, Middlesex TW8 9GS (GB)**

Remarks:

This application was filed on 18 - 10 - 2002 as a
divisional application to the application mentioned
under INID code 62.

(72) Inventors:
• **Blackler, Paul David James,
c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)**

(54) **Thiazolidinedione derivative and its use as antidiabetic**

(57) A polymorphic form of 5-[4-(2-(N-methyl-N-(2-pyridyl)amino)ethoxy)benzyl]thiazolidine-2,4-dione, maleic acid salt (the "Polymorph") characterised in that it provides:

- (i) an infra red spectrum containing peaks at 1752, 1546, 1154, 621, and 602 cm⁻¹; and/or
- (ii) a Raman spectrum containing peaks at 1751, 1243 and 602 cm⁻¹; and/or
- (iii) a solid-state nuclear magnetic resonance spectrum containing peaks at 111.9, 114.8, 119.6, 129.2, 134.0, 138.0, 144.7, 153.2, 157.1, 170.7, 172.0 and 175.0 ppm; and/or

(iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings of 6.46, 5.39, 4.83, 4.68, 3.71, 3.63, 3.58, and 3.48 Angstroms.; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

EP 1 277 753 A1

Description

[0001] This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

[0002] International Patent Application, Publication Number WO94/05659 discloses certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

[0003] International Patent Applications, Publication Numbers WO99/31093, WO99/31094 and WO99/31095 each disclose distinct hydrates of Compound (I).

[0004] It has now been discovered that Compound (I) exists in a novel polymorphic form which is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

[0005] The novel polymorphic form ('the Polymorph') also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

[0006] Accordingly, the present invention provides a polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt characterised in that it:

(i) provides an infra red spectrum containing peaks at 1752, 1546, 1154, 621, and 602 cm^{-1} ; and/or

(ii) provides a Raman spectrum containing peaks at 1751, 1243 and 602 cm^{-1} ; and/or

(iii) provides a solid-state nuclear magnetic resonance spectrum containing peaks at 111.9, 114.8, 119.6, 129.2, 134.0, 138.0, 144.7, 153.2, 157.1, 170.7, 172.0 and 175.0 ppm;

and/or

(iv) provides an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings of 6.46, 5.39, 4.83, 4.68, 3.71, 3.63, 3.58, and 3.48 Angstroms.

[0007] In one favoured aspect, the Polymorph provides an infrared spectrum substantially in accordance with Figure I.

[0008] In one favoured aspect, the Polymorph provides a Raman spectrum substantially in accordance with Figure II.

[0009] In one favoured aspect, the Polymorph provides a solid-state nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.

[0010] In one favoured aspect, the Polymorph provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.

[0011] The present invention encompasses the Polymorph isolated in pure form or when admixed with other materials, for example the known forms of Compound I or any other material.

[0012] Thus in one aspect there is provided the Polymorph in isolated form.

[0013] In a further aspect there is provided the Polymorph in pure form.

[0014] In yet a further aspect there is provided the Polymorph in crystalline form. The invention also provides a process for preparing the Polymorph, characterised in that a solution of Compound (I) in denatured ethanol at an elevated temperature, preferably in the range of from 65 °C to 70 °C for example 67.5 °C, is cooled preferably to a temperature in the range of from 20 °C to 25 °C, so as to provide crystallisation of the Polymorph. Preferably, the solution is filtered prior to cooling. In the above-mentioned process the solution may be seeded with the Polymorph to induce crystallisation but this is not essential.

[0015] The Polymorph is then recovered from the denatured ethanol. The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60 °C or 70 °C.

[0016] Conveniently the Polymorph is recovered from the denatured ethanol by filtration and subsequent drying.

[0017] In a further aspect, the invention provides a process for converting Polymorph to Compound (I), wherein a solution of Polymorph in a suitable solvent, such as acetone or ethanol, is seeded with Compound (I); preferably the reaction is carried out in an inert atmosphere, such as nitrogen. Generally, the solution of Polymorph is obtained by dissolving Polymorph at an elevated temperature in the solvent, such as acetone or ethanol.

[0018] Compound (I) is prepared according to known procedures, such as those disclosed in WO94/05659. The disclosures of WO94/05659 are incorporated herein by reference

For the avoidance of doubt the term "Compound (I)" as used herein refers to the form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt as disclosed and characterised in International Patent Application, Publication Number WO94/05659.

When used herein "denatured ethanol" means ethanol containing small amounts of methanol, usually up to 5% v/v of methanol, such as from 0.9% v/v to 5% v/v of methanol, for example ethanol containing 4% v/v of methanol.

[0019] When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment

31
128

EP 1 277 753 A1

[0036] In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

[0037] In addition, the Polymorph may be used in combination with other antidiabetic agents such as Insulin secretagogues, for example sulphonylureas, biguanides, such as metformin, alpha glucosidase inhibitors, such as acarbose, beta agonists, and insulin such as those disclosed in WO98/57649, WO98/57634, WO98/57635 or WO98/57636. The other antidiabetic agents, the amounts thereof and methods of administration are as described in the above mentioned publications. The formulation of the Polymorph and dosages thereof in said combinations are generally as disclosed for Compound (I) in the above mentioned publications. As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

[0038] 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.

[0039] The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Polymorph to a human or non-human mammal in need thereof.

[0040] Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

[0041] In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken in doses, such as those described above.

[0042] Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

[0043] In a further aspect the present invention provides the use of the Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

[0044] No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

[0045] The following example illustrates the invention but do not limit it in any way.

Example 1: Preparation of the Polymorph.

[0046] A mixture of maleic acid (2.10 g) and 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione (6.0 g) were heated to 70°C in denatured ethanol (60 ml, 5% v/v methanol) until complete dissolution was obtained. The resultant solution was filtered, re-heated to 67.5°C, and then cooled to 20-25°C. The resulting crystalline product was filtered off, washed with denatured ethanol (10 ml) and dried at 50°C *in vacuo* to give the Polymorph (6.61 g, 83%).

Example 2: Conversion of Polymorph to Compound (I)

[0047] Polymorph (10.0 g) was added to denatured ethanol (90 ml) under nitrogen. The resulting mixture was stirred and heated to 68°C, and held at this temperature for 30 min. The solution was hot filtered to a preheated vessel (56°C) and the filter washed with hot denatured ethanol (10ml). The temperature of the filtrate was adjusted to 60°C and then cooled with stirring. At 55°C the solution was seeded with Compound (I) (0.4 g) and cooling, with stirring, continued. The resulting slurry was stirred at ambient temperature for 1 h, and the solid isolated by filtration, washed with denatured ethanol and dried at 50°C *in vacuo* to give 8.4 g (84%) Compound (I).

Example 3: Conversion of Polymorph to Compound (I)

[0048] Polymorph (5.0 g) was added to acetone (170 ml) and the mixture was stirred and heated to reflux temperature. After complete dissolution, the solution was heated at reflux for 30min, then filtered. The filtered solution was concentrated by distillation at atmospheric pressure (120ml of distillate was collected). The remaining solution was stirred and cooled at about 1°C/min and at 50°C seeded with Compound (I) (0.2 g). Cooling was continued at 1°C/min, and when the slurry reached 20°C stirring was continued for 1 h. The solid was isolated by filtration, washed with acetone and dried *in vacuo* at 50°C to give 4.2 g (84%) of Compound (I).

CHARACTERISING DATA: The following characterising data were generated for the polymorph:

A Infrared

[0049] The infrared absorption spectrum of a mineral oil dispersion of the Polymorph was obtained using a Nicolet

12932

EP 1 277 753 A1

Table II (continued)

X-Ray Powder Diffraction Angles and Calculated Lattice Spacings Characteristic of the Polymorph.	
Diffraction Angle ($^{\circ}2\theta$)	Lattice Spacing (Angstroms)
14.0	6.32
14.7	6.03
14.9	5.95
15.3	5.77
16.4	5.39
18.4	4.83
18.7	4.74
19.0	4.68
19.3	4.59
20.0	4.44
21.0	4.22
21.9	4.07
22.5	3.94
23.3	3.81
24.0	3.71
24.5	3.63
24.9	3.58
25.6	3.48
26.2	3.40
27.2	3.28
27.7	3.22
28.7	3.11
29.2	3.05
29.6	3.02
30.2	2.96
30.8	2.90
31.0	2.88
31.7	2.82
32.3	2.77
32.9	2.72
33.4	2.68
34.2	2.62

Claims

1. A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the Polymorph) characterised in that it provides:
 - (i) an infra red spectrum containing peaks at 1782, 1546, 1154, 621, and 602 cm^{-1} ; and/or
 - (ii) a Raman spectrum containing peaks at 1751, 1243 and 602 cm^{-1} ; and/or
 - (iii) a solid-state nuclear magnetic resonance spectrum containing peaks at 111.9, 114.8, 119.6, 129.2, 134.0, 138.0, 144.7, 153.2, 157.1, 170.7, 172.0 and 175.0 ppm; and/or
 - (iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings of 6.46, 5.39, 4.83, 4.68, 3.71, 3.63, 3.58, and 3.48 Angstroms.
2. A Polymorph according to claim 1, which provides an infra red spectrum substantially in accordance with Figure 1.
3. A Polymorph according to claim 1 or claim 2, which provides a Raman spectrum substantially in accordance with Figure 2.

EP 1 277 753 A1

4. A Polymorph according to any one of claims 1 to 3, which provides a solid-state nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.
5. A Polymorph according to any one of claims 1 to 4, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.
6. A Polymorph according to any one of claims 1 to 5, in isolated form.
7. A Polymorph according to any one of claims 1 to 6, in pure form.
8. A Polymorph according to any one of claims 1 to 7, in crystalline form.
9. A process for preparing a Polymorph according to claim 1, characterised in that a solution of Compound (I) in denatured ethanol at an elevated temperature is cooled so as to provide crystallisation of the Polymorph after which the Polymorph is recovered from the denatured ethanol.
10. A pharmaceutical composition comprising an effective, non-toxic amount of a Polymorph according to claim 1 and a pharmaceutically acceptable carrier therefor.
11. A Polymorph according to claim 1, for use as an active therapeutic substance.
12. A Polymorph according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
13. The use of Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
14. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph to a human or non-human mammal in need thereof.

34
131

(19)  **Europäisches Patentamt**
European Patent Office
Office européen des brevets



(11) **EP 1 284 268 A1**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
19.02.2003 Bulletin 2003/08

(51) Int Cl.7: **C07D 417/12, A61K 31/427,
A61P 3/10**

(21) Application number: **02080320.1**

(22) Date of filing: **19.04.2000**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**
Designated Extension States:
AL LT LV MK RO SI

- **Giles, Robert Gordon, c/o GlaxoSmithKline**
Near Leigh Tonbridge, Kent TN11 9AN (GB)
- **Sasse, Michael John, c/o GlaxoSmithKline**
Near Leigh Tonbridge, Kent TN11 9AN (GB)

(30) Priority: **23.04.1999 GB 9909472**
25.05.1999 GB 9912197

(74) Representative: **Rutter, Keith et al**
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.1)
980 Great West Road
Brentford, Middlesex TW8 9GS (GB)

(62) Document number(s) of the earlier application(s) in
accordance with Art. 76 EPC:
00920889.3 / 1 173 434

Remarks:

This application was filed on 18 - 10 - 2002 as a
divisional application to the application mentioned
under INID code 62.

(71) Applicant: **SMITHKLINE BEECHAM PLC**
Brentford, Middlesex TW8 9GS (GB)

(72) Inventors:
• **Blackler, Paul David James,**
c/o GlaxoSmithKline
Near Leigh Tonbridge, Kent TN11 9AN (GB)

(54) **Thiazolidinedione derivative and its use as antidiabetic**

(57) A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the "Polymorph") characterised in that it:

- (i) provides an infra red spectrum containing peaks at 1360, 1326, 1241, 714 and 669 cm⁻¹; and/or
- (ii) provides a Raman spectrum containing peaks at 1581, 768, 670, 271 and 226 cm⁻¹; and/or
- (iii) provides a solid-state nuclear magnetic resonance spectrum containing peaks at chemical shifts substantially as set out in Table I; and/or

(iv) provides an X-ray powder diffraction (XRPD) pattern containing peaks substantially as set out in Table II; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

EP 1 284 268 A1

Description

[0001] This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

[0002] International Patent Application, Publication Number WO94/05659 discloses certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activity including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)").

[0003] International Patent Applications, Publication Numbers WO99/31093, WO99/31094 and WO99/31095 each disclose distinct hydrates of Compound (I).

[0004] It has now been discovered that Compound (I) exists in a novel polymorphic form which is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

[0005] The novel polymorphic form ('the Polymorph') also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

[0006] Accordingly, the present invention provides a polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt characterised in that it:

- (i) provides an infra red spectrum containing peaks at 1360, 1326, 1241, 714 and 669 cm^{-1} ; and/or
- (ii) provides a Raman spectrum containing peaks at 1581, 768, 670, 271 and 226 cm^{-1} ; and/or
- (iii) provides a solid-state nuclear magnetic resonance spectrum containing peaks at chemical shifts substantially as set out in Table I; and/or
- (iv) provides an X-ray powder diffraction (XRPD) pattern containing peaks substantially as set out in Table II.

[0007] In one favoured aspect, the Polymorph provides an infrared spectrum substantially in accordance with Figure I.

[0008] In one favoured aspect, the Polymorph provides a Raman spectrum substantially in accordance with Figure II.

[0009] In one favoured aspect, the Polymorph provides a solid-state nuclear magnetic resonance spectrum substantially in accordance with Figure III.

[0010] In one favoured aspect, the Polymorph provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV.

[0011] The present invention encompasses the Polymorph isolated in pure form or when admixed with other materials, for example the known forms of Compound I or any other material.

[0012] Thus in one aspect there is provided the Polymorph in isolated form.

[0013] In a further aspect there is provided the Polymorph in pure form.

[0014] In yet a further aspect there is provided the Polymorph in crystalline form.

[0015] The invention also provides a process for preparing the Polymorph, characterised in that a slurry of Compound (I) in aqueous ethanol containing up to about 2.5% w/v water, preferably aqueous denatured ethanol containing up to about 2.5% w/v water, for example 2.5% w/v water, is heated, suitably to a temperature in the range of from 35°C and 60°C, such as 40°C to 50°C, for example to 45°C, for an extended period of time, for example 65 hours, after which time the Polymorph is recovered from the denatured ethanol. Optionally, the reaction mixture is seeded with the Polymorph.

[0016] In a further process of the invention, Compound (I) is admixed with denatured ethanol, heated to an elevated temperature, preferably a temperature in the range of from 35°C and 60°C, such as 40°C to 50°C, for example from 45°C to 47°C, over an extended period of time, for example 65 hours, after which time the Polymorph is recovered from the solvent. Optionally, the reaction mixture is seeded with Polymorph.

[0017] In a further process a solution of Compound (I) in denatured ethanol containing up to 2.5% w/v water, for example 0.8 to 2.5% w/v water, at 55°C is seeded with the Polymorph then cooled to a temperature in the range of from 20°C to 25°C to provide the Polymorph. The Polymorph is then recovered from the denatured ethanol.

[0018] The solution of Compound (I) in the denatured ethanol is conveniently prepared by dissolving Compound (I) in the required amount of denatured ethanol at an elevated temperature, for example 60°C. In our hands this latter process is also effectively carried out using Compound (I) containing up to 25% w/w of the hydrate disclosed in WO99/31093 mentioned above.

[0019] Conveniently the Polymorph is recovered from the reaction solvent, such as denatured ethanol, by filtration and subsequent drying, preferably at an elevated temperature, for example 45°C.

[0020] In a further aspect the present invention also provides a process for preparing Compound (I) (also for convenience referred to as the "Original Polymorph") from the Polymorph of the invention, which process comprises first preparing a solution of the Polymorph in a mixture (100:1v/v) of absolute ethanol and methanol, at an elevated tem-

use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

[0040] For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

[0041] Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

[0042] In addition such compositions may contain further active agents such as anti-hypertensive agents and diuretics.

[0043] In addition, the Polymorph may be used in combination with other antidiabetic agents such as insulin secretagogues, for example sulphonylureas, biguanides, such as metformin, alpha glucosidase inhibitors, such as acarbose, beta agonists, and insulin such as those disclosed in WO98/57649, WO98/57634, WO98/57635 or WO98/57636. The other antidiabetic agents, the amounts thereof and methods of administration are as described in the above mentioned publications. The formulation of the Polymorph and dosages thereof in said combinations are generally as disclosed for Compound (I) in the above mentioned publications. As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

[0044] 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 veterinary acceptable salt.

[0045] The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Polymorph to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition herein before defined, and this forms a particular aspect of the present invention.

[0046] In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof the Polymorph may be taken in doses, such as those described above.

[0047] Similar dosage regimens are suitable for the treatment and/or prophylaxis of non-human mammals.

[0048] In a further aspect the present invention provides the use of the Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

[0049] No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

[0050] The following examples illustrate the invention but do not limit it in any way.

Examples:

[0051] Example 1: A slurry of Compound (I) (3.0 g, prepared as per WO94/05659 in denatured ethanol (30.5 ml, water content 2.5% w/v)) was heated at 45°C for 65 hours. The product was filtered at 45°C and dried at 50°C *in vacuo* to give the Polymorph (1.55 g).

[0052] Example 2: To a mixture of absolute ethanol (30 ml, water <0.1% w/v) and methanol (1.2 ml) was added Compound (I) (2.00 g). The resulting suspension was heated to 45-7°C and maintained at this temperature for 65h. The solid was isolated at 45°C and dried at 50°C *in vacuo* to give 0.83 g (41%) of Polymorph.

[0053] Example 3: Compound (I) (6.0 g, containing approximately 25% w/w of the hydrate disclosed in WO99/31093) was heated at 60°C in denatured ethanol (60 ml, water content 0.8% w/v) until complete dissolution was obtained. The resultant solution was cooled to 55°C, seeded with the title compound (0.06 g), then cooled to 20-25°C. The product was filtered, washed with denatured ethanol (10 ml) and dried at 50°C *in vacuo* to give the Polymorph (4.8 g, 80%).

[0054] Example 4: Conversion of the Polymorph to Compound (I) (the Original Polymorph): The Polymorph (4.0 g) was heated to 68°C in a mixture of absolute ethanol (40 ml) and methanol (0.4 ml) until complete dissolution was

(continued)

Start angle	3.5 °2 θ
End angle	35.0 °2 θ
Step size	0.020 °2 θ
Time per step	2.3 s

Table II.

X-Ray Powder Diffraction Angles and Calculated Lattice Spacings Characteristic of the Polymorph.	
Diffraction Angle (°2 θ)	Lattice Spacing (Angstroms)
8.9	9.90
12.0	7.35
14.0	6.32
15.4	5.73
15.9	5.55
16.8	5.26
17.4	5.08
18.1	4.89
19.2	4.60
19.6	4.52
20.0	4.44
20.3	4.37
20.8	4.27
21.2	4.18
22.3	3.97
23.7	3.80
24.3	3.75
25.1	3.54
25.8	3.44
26.7	3.33
27.2	3.27
28.7	3.10
29.6	3.01
30.6	2.92
31.6	2.83
32.2	2.78
33.3	2.69

Claims

1. A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the "Polymorph") characterised in that it:
 - (i) provides an infra red spectrum containing peaks at 1360, 1326, 1241, 714 and 669 cm⁻¹; and/or
 - (ii) provides a Raman spectrum containing peaks at 1581, 768, 670, 271 and 226 cm⁻¹; and/or
 - (iii) provides a solid-state nuclear magnetic resonance spectrum containing peaks at chemical shifts substantially as set out in Table I; and/or
 - (iv) provides an X-ray powder diffraction (XRPD) pattern containing peaks substantially as set out in Table II.
2. A Polymorph according to claim 1, which provides an infra red spectrum substantially in accordance with Figure 1.
3. A Polymorph according to claim 1 or claim 2, which provides a Raman spectrum substantially in accordance with

Figure II.

4. A Polymorph according to any one of claims 1 to 3, which provides a solid-state nuclear magnetic resonance spectrum substantially in accordance with Figure III.
5. A Polymorph according to any one of claims 1 to 4, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV.
6. A Polymorph according to any one of claims 1 to 5, in isolated form.
7. A Polymorph according to any one of claims 1 to 6, in pure form.
8. A Polymorph according to any one of claims 1 to 7, in crystalline form.
9. A process for preparing a Polymorph according to claim 1, characterised in that:
 - (a) a slurry of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (hereinafter also referred to as "Compound (I)" or the "Original Polymorph") in aqueous ethanol containing up to about 2.5% w/v water, is heated for an extended period of time; after which time the Polymorph is recovered from the denatured ethanol; or
 - (b) Compound (I) is admixed with denatured ethanol, heated to an elevated temperature, over an extended period of time, after which time the Polymorph is recovered from the solvent; or
 - (c) Compound (I) in denatured ethanol containing up to 2.5% w/v water at 55°C is seeded with the Polymorph then cooled to a temperature in the range of from 20°C to 25°C to provide the Polymorph;the Polymorph is then recovered from the solvent..
10. A pharmaceutical composition comprising an effective, non-toxic amount of a Polymorph according to claim 1 and a pharmaceutically acceptable carrier therefor.
11. A Polymorph according to claim 1, for use as an active therapeutic substance.
12. A Polymorph according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
13. The use of Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
14. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph to a human or non-human mammal in need thereof.

morfología de la superficie de las partículas que constituyen dicha sustancia activa. Por ello, tiene gran interés en la fase de preformulación el análisis granulométrico, que proporciona información sobre el tamaño medio de las partículas, su homogeneidad y la forma de las mismas.

Las técnicas de análisis granulométrico habitualmente utilizadas son la microscopia óptica y la tamización analítica. Y para conocer directamente la superficie específica se emplea la técnica de adsorción de gases.

Para utilizar la microscopia óptica es necesario acondicionar previamente la muestra. Se prepara una suspensión de las partículas en un líquido de índice de refracción adecuado y en el que sean prácticamente insolubles. Se deposita una gota de la suspensión entre un portaobjetos y un cubreobjetos y la muestra así preparada se observa al microscopio. Para medir las partículas correctamente el microscopio debe llevar acoplado un ocular Watson. El número de partículas que hay que medir será como mínimo 100. Las partículas, según su tamaño, se agrupan en intervalos cuya amplitud seguirá una progresión previamente fijada y constante.

Cada vez tiene más auge la utilización de técnicas de difracción de rayo láser y de espectroscopia de correlación fotónica.

1.4.4. Cristalinidad y polimorfismo

En la figura 1.9 se recogen algunas de las diferentes posibilidades en las que se puede presentar una sustancia al estado sólido. El hábito cristalino y la estructura interna de una sustancia activa puede afectar a alguna de sus características tales como fluidez y estabilidad química. Hábito cristalino es la descripción del aspecto externo de los cristales, mientras que la estructura interna es la disposición de los elementos dentro del sólido. Una sustancia con una misma estructura cristalina interna puede presentarse con diferentes hábitos cristalinos en función de las condiciones en que ha cristalizado.

Por otro lado, se ha de diferenciar en la estructura interna de una sustancia al estado sólido las dos posibilidades de sustancia cristalina y amorfa. En la sustancia cristalina se repite a lo largo de las tres dimensiones del espacio la disposición de los átomos, moléculas o iones. En la sustancia amorfa no aparece esta ordenación. En ocasiones se puede conseguir que una sustancia solidifique al estado amorfo a partir de una disolución mediante precipitación o enfriamiento rápidos o por un proceso de liofilización.

Las sustancias amorfas son inestables y tienden a transformarse en cristalinas en un período de tiempo más o menos prolongado. Dado que sus características de fusión, disolución, etc., son diferentes (hay que aportar más energía para fundir o disolver una sustancia cristalina que una amorfa), en el período de reposición de las formas farmacéuticas se podría producir este cambio, con lo que se verían afectadas sus características macroscópicas (disoluciones que precipitan, creci-

miento cristalino en suspensiones y supositorios), así como su proceso de absorción, es decir, su biodisponibilidad. Esto constituye el mayor inconveniente al incluir una sustancia amorfa en una forma de dosificación.

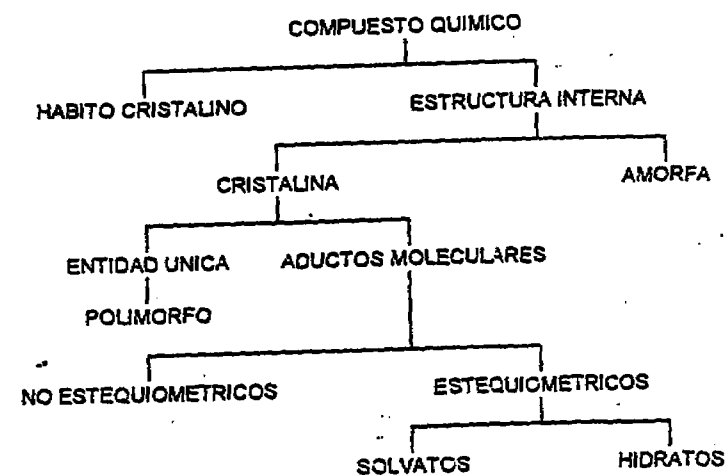


FIGURA 1.9. Diferentes posibilidades en que puede aparecer un compuesto químico al estado sólido.

Un compuesto cristalino puede cristalizar con una determinada cantidad de disolvente. Si el disolvente de cristalización no está en proporciones estequiométricas con la sustancia activa, esta posibilidad al estado sólido se debe rechazar, por las dificultades que entraña su reproductibilidad. Si el disolvente de cristalización está en proporciones estequiométricas, origina los solvatos, de los cuales sólo se incluirán en el estudio de preformulación los hidratos.

La identificación de los hidratos es importante, porque sus parámetros de solubilidad pueden ser significativamente inferiores a los de las formas anhidras, lo que podría redundar en la velocidad y cantidad de fármaco absorbido, al incluir el hidrato en una forma farmacéutica.

En múltiples ocasiones cuando se inicia la preformulación no se tienen tipificadas todas las posibles formas al estado sólido del principio activo y es posible la aparición de diversos polimorfos. "Polimorfismo" es un término técnico que se utiliza en Biología y en Cristalografía para describir el hecho de que un fenómeno natural pueda tener lugar de dos o más formas diferentes.

En Cristalografía el polimorfismo se refiere a materiales cristalinos naturales o sintéticos. Si una sustancia se presenta en dos formas cristalinas, a una tempera-

tura dada, sólo una es estable y la otra es la forma inestable o metastable. A veces hay más de dos formas cristalinas, como es el caso del fenobarbital, del que se han identificado hasta once formas diferentes; para su denominación se comienza adjudicándole el término I al polimorfo de mayor punto de fusión, y II, III, etc., a los que presentan puntos de fusión en orden decreciente.

La importancia que puede tener el que un fármaco posea dos o más formas cristalinas se debe a que, al ser entidades químicamente idénticas, pero físicamente diferentes, las características que derivan de su estructura al estado sólido también difieren. Así, presentarán no sólo diferente punto de fusión, sino que también pueden tener diferente densidad, capacidad para fluir, compresibilidad, calores de fusión y disolución, solubilidad, etc. Estas diferencias pueden originar dificultades en los procesos tecnológicos de elaboración de las formas farmacéuticas cuando se pase de utilizar un polimorfo a otro. Asimismo, si se trabaja con la forma metastable es probable que durante el almacenamiento de algunas formas farmacéuticas se produzca la transición hacia la más estable, originando, como en el caso de la transición amorfo/cristalino, dificultad en redispersión cuando se trata de suspensiones, crecimiento cristalino, etc.

Por lo anteriormente expuesto, el fenómeno del polimorfismo puede provocar alteraciones relativas a la biodisponibilidad del fármaco en función del polimorfo que, incluido en la forma farmacéutica, se administra al organismo. La utilización del polimorfo que tenga mayor solubilidad puede proporcionar niveles sanguíneos suficientes para obtener una acción terapéutica, mientras que la forma estable al disolverse más lentamente y en menor proporción puede dar lugar a concentraciones en sangre que resulten insuficientes para lograr una acción terapéutica. Este hecho se ha puesto de manifiesto en diferentes ocasiones. Así, del palmitato de cloranfenicol se conocen dos polimorfos denominados A y B (según la nomenclatura indicada anteriormente les correspondería la denominación I y II). El polimorfo A, más estable y de mayor punto de fusión, presenta menor biodisponibilidad que el polimorfo B, inestable, de menor punto de fusión y mayor solubilidad.

Las fases que hay que seguir para investigar el polimorfismo en la nueva molécula serían:

- Recristalización a partir de los disolventes habitualmente empleados en las últimas etapas de la síntesis y en los procesos tecnológicos de elaboración de formas farmacéuticas.
- Identificación de los cristales obtenidos mediante difracción de rayos X y al menos otra técnica de evaluación del polimorfismo como espectroscopia de infrarrojos, calorimetría diferencial de barrido, microscopia, etc.
- Si se confirma la existencia de polimorfos, se cuantifican las características fisicoquímicas que pueden afectar a la biodisponibilidad, estabilidad y reproducibilidad de los procesos de fabricación. Así se determinaría el perfil de solubilidad, estabilidad, morfología cristalina, comportamiento calorimétrico y perfil de humedades de equilibrio.

- Si los resultados indican que las propiedades físicas de los polimorfos hallados pueden afectar a la calidad y/o la biodisponibilidad del fármaco a partir de la forma de dosificación, es necesario desarrollar un proceso reproducible para sintetizar siempre el polimorfo deseado. Si no se puede evitar en la síntesis la mezcla de polimorfos, es necesario realizar un control cuantitativo, previamente validado, para asegurar la proporción de polimorfos.

Actualmente, en los laboratorios farmacéuticos, las técnicas analíticas que se utilizan para caracterizar el estado sólido y detectar así la posible presencia de polimorfos, amorfos, hidratos, etc., son las que se indican a continuación.

Las técnicas de microscopia óptica y electrónica de barrido sirven para distinguir la forma y el aspecto de las partículas; luego proporcionarán información sobre el hábito cristalino y detectarán las sustancias amorfas. La microscopia electrónica de barrido no es una técnica rutinaria dentro del laboratorio farmacéutico por la dificultad que entraña la preparación de la muestra y lo costoso que resulta el manejo y mantenimiento de los equipos.

Existen también distintas técnicas de análisis térmico:

- La microscopia de platina caliente permite detectar visualmente los cambios que sufre una muestra durante el aporte de calor. Entre otros fenómenos se puede determinar cualitativamente la pérdida de disolvente de cristalización, las transformaciones cristalinas, los procesos de fusión y recristalización, la sublimación y recristalización, la descomposición, etc.
- La calorimetría diferencial de barrido (DSC) cuantifica los procesos que sufre una muestra durante su calentamiento, indicando si el proceso es endotérmico (pérdida de disolvente, fusión, etc.) o exotérmico (recristalización, descomposición, etc.). Asimismo, permite detectar la presencia de impurezas, dado que uno de los datos que se pueden calcular por calorimetría diferencial de barrido es la pureza de la sustancia analizada.
- La termogravimetría mide los cambios de peso que experimenta la muestra al aumentar la temperatura o a lo largo del tiempo a una temperatura determinada.

En la figura 1.10 se recogen las curvas de DSC correspondientes a dos polimorfos y un hidrato de la prednisolona.

La técnica de difracción de rayos X en polvo proporciona un espectro que es característico de la sustancia activa e indica si es amorfo o cristalino. Al ser una técnica no destructiva, permite su utilización en la caracterización incluso de sustancias cuyo tamaño de lote es muy reducido. Cuando existen dudas sobre una posible recristalización a partir de un amorfo, o de transformación de un polimorfo en otro, esta técnica proporciona resultados concluyentes, puesto que se dice

que el espectro de rayos X es como la huella digital de cualquier compuesto en estado sólido.

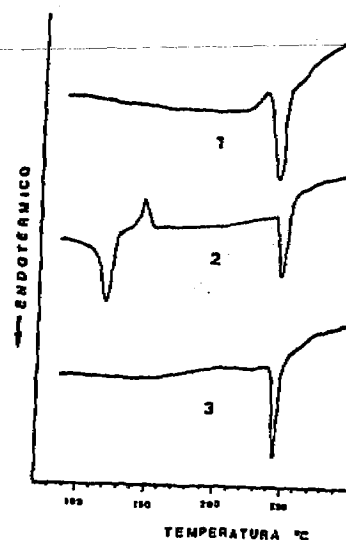


FIGURA 1.10. Curvas de DSC de prednisolona: (1) forma I, anhidra; (2) hidrato de la forma I; (3) forma II.

En la figura 1.10 se recogen los espectros de difracción de rayos X de las diferentes formas de ampicilina según la Farmacopea de los Estados Unidos de 1995 (USP 23).

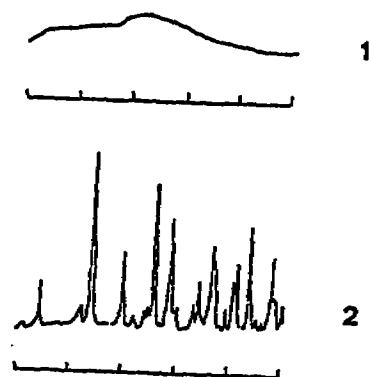


FIGURA 1.11. Espectros de difracción de rayos X de cuatro formas sólidas de ampicilina (USP 23): (1) ampicilina amorfa (anhidra), (2) ampicilina trihidrato.

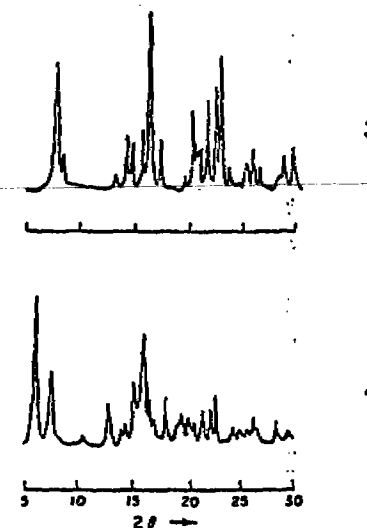


FIGURA 1.11. (continuación) (3) polimorfo 1 de ampicilina anhidra, (4) polimorfo 2 de ampicilina anhidra.

1.4.5. Punto de fusión

La determinación del punto de fusión de un principio activo puede medirse utilizando fundamentalmente tres técnicas:

- Método del capilar.
- Microscopia de platina caliente.
- Calorimetría diferencial de barrido.

El método del capilar consiste en la observación directa, o bajo lupa, de la muestra introducida en un capilar, el cual se encuentra en contacto con una pieza metálica con calentamiento programado. Así se obtiene información sobre el intervalo de fusión, pero resulta difícil determinar de forma exacta el punto de fusión.

La microscopia de platina caliente permite la observación microscópica de las partículas, tal y como se indicó en el apartado de polimorfismo. El microscopio va equipado con una platina que se calienta a una velocidad controlable y se puede registrar el inicio de la fusión, la temperatura a la que funde la mitad de la muestra y la fusión total.

La calorimetría diferencial de barrido proporciona, no sólo el punto de fusión exacto, sino también el calor de fusión. La presencia de impurezas se detecta con este método de análisis térmico como se ha comentado anteriormente. En la figura 1.12 se recogen las curvas de DSC del ácido benzoico con diferentes grados de impurezas.

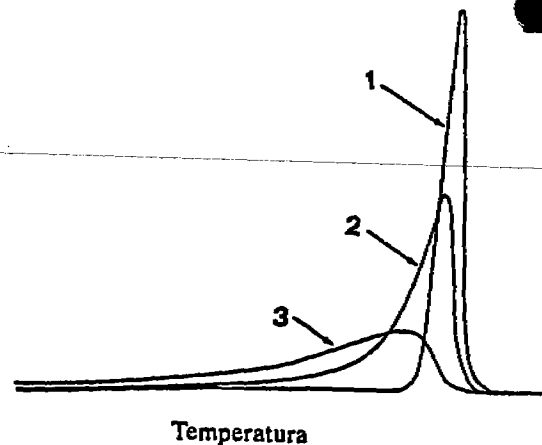


FIGURA 1.12. Curvas de DSC correspondientes al ácido benzoico: (1) ácido benzoico patrón, (2) ácido benzoico con una pureza del 98,6%, (3) ácido benzoico con una pureza del 97,2%.

1.4.6. Solubilidad

Uno de los estudios de mayor interés en preformulación es el dedicado al conocimiento de la disolución del fármaco, etapa previa a su absorción. Tanto si el posible fármaco se va a incluir en una forma sólida como en una forma líquida, la disolución es un proceso que siempre se llevaría a cabo, bien después de la administración (formas sólidas), inmediatamente antes de ésta (formas de disolución extemporánea) o en la etapa de fabricación (formas líquidas).

Se ha observado que los fármacos que presentan baja solubilidad en fluidos acuosos a menudo presentan una absorción escasa o errática. Asimismo, las variaciones en niveles plasmáticos interindividuales e intraindividuales que se obtienen después de la administración oral suelen ser bastante frecuentes en el caso de fármacos poco hidrosolubles.

El polimorfismo, el grado de hidratación, la cristalinidad, así como el que el fármaco se presente como una u otra sal son factores que condicionan su solubilidad. En consecuencia, los estudios de solubilidad, sobre todo de fármacos poco solubles, se diseñarán teniendo en cuenta los factores citados. Los estudios de solubilidad en la etapa de preformulación incluyen:

- Determinación de pKa.
- Influencia de la temperatura.
- Perfil de solubilidad en función del pH.
- Coeficiente de reparto.
- Mecanismos de solubilización.
- Velocidad de disolución.

Al realizar un estudio de solubilidad o de velocidad de disolución se han de prefiar factores como la temperatura, el pH del medio, la composición del medio, etc. Para determinar la solubilidad en equilibrio de un soluto en un disolvente, se mantiene un exceso de soluto en el disolvente elegido a temperatura constante. Después de transcurrido un período de tiempo suficiente para alcanzar la saturación, se procede a filtrar el líquido y se evalúa la cantidad de soluto disuelto. Si el soluto es un líquido inmiscible (líquido oleoso), hay que recurrir a la centrifugación para eliminar la fracción no disuelta.

En el caso de sustancias no estables en medio acuoso, la determinación de su solubilidad se realizará de forma similar, pero los datos obtenidos serán evaluados de forma diferente a la habitual para evitar errores.

Los estudios de solubilidad se suelen hacer en agua, ClH 0,01M, ClH 0,1M y NaOH 0,1M, todos a temperatura ambiente, así como en solución amortiguadora de pH 7,4 a 37 °C. Estos últimos datos son útiles cuando se vayan a preparar formulaciones como suspensiones y disoluciones para estudios farmacológicos y de toxicidad.

Los estudios de solubilidad *in vitro* no predicen la acción biológica de una sustancia, pero proporcionan información útil para los posteriores estudios *in vivo* y para la etapa de desarrollo, antes de evaluar el fármaco en seres humanos.

A) Determinación de pKa

En el caso de sustancias con carácter ácido o básico débil, la determinación de su pKa reviste gran interés, dado que la relación numérica entre el pKa del fármaco y el pH del medio condiciona su grado de ionización y, como es sabido, en términos generales, sólo las formas no ionizadas son susceptibles de absorción a través de membrana.

En los ácidos carboxílicos la forma ionizada absorbe con frecuencia en la región del ultravioleta y su concentración puede determinarse por espectrofotometría directa. La forma no ionizada absorberá a diferente longitud de onda, de forma que la relación forma ionizada/forma no ionizada podrá determinarse en una serie de soluciones amortiguadoras de diferentes valores de pH. Así, el valor del pKa corresponderá a la ordenada al origen que se obtiene al representar el pH frente al logaritmo de la relación fracción ionizada/fracción no ionizada, según la ecuación de Hendersson-Hasselbach:

$$pH = pK + \log (A^-/AH) \quad [1.2]$$

B) Influencia de la temperatura

En la mayoría de los casos, la disolución es un proceso endotérmico; por tanto, al aumentar la temperatura, aumentará el parámetro solubilidad. Pero no pue-

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 05-97262

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 573 DE

FECHA 28 DE FEBRERO DE 2007 EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL 30 DE MAYO DEL 2007

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO **X**

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 277 753 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:
22.01.2003 Bulletin 2003/04

(51) Int Cl.7: C07D 417/12, A61K 31/427,
A61P 3/10

(21) Application number: 02000319.3

(22) Date of filing: 19.04.2000

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

- Giles, Robert Gordon, c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)
- Moore, Stephen, c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)
- Sasse, Michael, John c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)

(30) Priority: 23.04.1999 GB 9909471
25.05.1999 GB 9912195

(74) Representative: Rutter, Keith et al
GlaxoSmithKline
Corporate Intellectual Property (CN9.25.1)
990 Great West Road
Brentford, Middlesex TW8 9GS (GB)

(62) Document number(s) of the earlier application(s) in
accordance with Art. 75 EPC:
00922793.5 / 1 175 418

(71) Applicant: SmithKline Beecham plc
Brentford, Middlesex TW8 9GS (GB)

Remarks:

This application was filed on 18 - 10 - 2002 as a
divisional application to the application mentioned
under INID code 62.

(72) Inventors:
• Blackler, Paul David James,
c/o GlaxoSmithKline
Tonbridge, Kent TN11 9AN (GB)

(54) Thiazolidinedione derivative and its use as antidiabetic

(57) A polymorphic form of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, maleic acid salt (the "Polymorph") characterised in that it provides:

- (i) an infra red spectrum containing peaks at 1752, 1546, 1154, 821, and 602 cm⁻¹; and/or
- (ii) a Raman spectrum containing peaks at 1751, 1243 and 602 cm⁻¹; and/or
- (iii) a solid-state nuclear magnetic resonance spectrum containing peaks at 111.9, 114.8, 119.6, 129.2, 134.0, 138.0, 144.7, 153.2, 157.1, 170.7, 172.0 and 175.0 ppm; and/or

(iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings of 6.46, 5.39, 4.83, 4.68, 3.71, 3.63, 3.58, and 3.48 Angstroms.; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

EP 1 277 753 A1

Table II (continued)

X-Ray Powder Diffraction Angles and Calculated Lattice Spacings Characteristic of the Polymorph.	
Diffraction Angle ($^{\circ}2\theta$)	Lattice Spacing (Angstroms)
14.0	6.32
14.7	6.03
14.9	5.95
15.3	5.77
16.4	5.39
18.4	4.83
18.7	4.74
19.0	4.68
19.3	4.59
20.0	4.44
21.0	4.22
21.9	4.07
22.5	3.94
23.3	3.81
24.0	3.71
24.5	3.63
24.9	3.58
25.6	3.48
26.2	3.40
27.2	3.28
27.7	3.22
28.7	3.11
29.2	3.05
29.6	3.02
30.2	2.96
30.8	2.90
31.0	2.88
31.7	2.82
32.3	2.77
32.9	2.72
33.4	2.68
34.2	2.62

Claims

1. A Polymorph of 5-(4-(2-(N-methyl-2-pyrrolidino)ethoxy)benzyl)thiazolidine-2-thione and/or salt (the Polymorph) characterized in that it provides:

- (i) an infra red spectrum containing peaks at 1752, 1548, 1154, 621, and 602 cm^{-1} ; and/or
- (ii) a Raman spectrum containing peaks at 1751, 1243 and 602 cm^{-1} ; and/or
- (iii) a solid-state nuclear magnetic resonance spectrum containing peaks at 111.9, 114.3, 119.6, 129.2, 134.0, 138.0, 144.7, 153.2, 157.1, 170.7, 172.0 and 175.0 ppm; and/or
- (iv) an X-ray powder diffraction (XRPD) pattern which gives calculated lattice spacings of 6.46, 5.39, 4.83, 4.68, 3.71, 3.63, 3.58, and 3.48 Angstroms.

2. A Polymorph according to claim 1, which provides an infra red spectrum substantially in accordance with Figure I.

3. A Polymorph according to claim 1 or claim 2, which provides a Raman spectrum substantially in accordance with Figure II.

4. A Polymorph according to any one of claims 1 to 3, which provides a solid-state nuclear magnetic resonance spectrum substantially in accordance with Figure III and/or Table I.
5. A Polymorph according to any one of claims 1 to 4, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure IV and/or Table II.
6. A Polymorph according to any one of claims 1 to 5, in isolated form.
7. A Polymorph according to any one of claims 1 to 6, in pure form.
8. A Polymorph according to any one of claims 1 to 7, in crystalline form.
9. A process for preparing a Polymorph according to claim 1, characterized in that a solution of Compound (I) in denatured ethanol at an elevated temperature is cooled so as to provide crystallization of the Polymorph after which the Polymorph is recovered from the denatured ethanol.
10. A pharmaceutical composition comprising an effective, non-toxic amount of a Polymorph according to claim 1 and a pharmaceutically acceptable carrier therefor.
11. A Polymorph according to claim 1, for use as an active therapeutic substance.
12. A Polymorph according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
13. The use of Polymorph for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.
14. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Polymorph to a human or non-human mammal in need thereof.

144
~~144~~

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
✓ **J. IAN RAISBECK LLINÁS**
Apoderado

ASUNTO	Radicación	05-097262
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	07 - 12871

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/GB2004/001306

Fecha de Presentación Interna. 25 de marzo de 2004

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 33 a 58 y 62 como se radicó inicialmente

Reivindicaciones: Folios 59 a 60 como se radicó inicialmente

Prioridad: Folios: 01
28 de marzo de 2003, GB, 0307259.2

Remisión de información: Folios: 98 a 139

2. Análisis de la Prioridad

La fecha de prioridad del 28 de marzo de 2003 y su correspondiente documento, corresponden con la materia solicitada de protección.

3. Objeto de la invención

Título de la solicitud: proceso para la preparación de un polimorfo de maleato de rosiglitazona.

El objeto de la presente solicitud de patente de invención consiste en la obtención de un procedimiento de preparación de un polimorfo de maleato de rosiglitazona y su correspondiente purificación.

El problema planteado en esta solicitud es la necesidad de proveer el polimorfo de maleato de rosiglitazona y su proceso de purificación.

Para solucionar este problema técnico la solicitud en estudio, el solicitante proporciona un procedimiento de preparación del polimorfo maleato de rosiglitazona, y su correspondiente purificación.

IPC: C07D 417/12

4. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

La reivindicación 1 se encuentra caracterizada de forma general y amplia, al referirse a los solventes empleados y sus propiedades como es la constante dieléctrica.

Se caracteriza, además, por su resultado final a alcanzar como es *que se encuentra substancialmente libre de cualquier otra forma polimórfica*; la cual además no es aceptada pues es claro que al final del proceso de obtención de polimorfos; se pueden obtener cantidades de otro(s) polimorfos.

La reivindicación 2 se refiere a los solventes a su constante dieléctrica, sin embargo no es claro a cuáles corresponde. Se encuentra además, de forma independiente de la reivindicación 1.

La reivindicación 4 se refiere a *una mezcla seleccionada entre acetato de etilo e IMS*; se sugiere al solicitante colocar éste último en su nombre genérico.

5. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486)

La reivindicación 12, se refiere al uso del polimorfo, la cual no es patentable de acuerdo a los artículos mencionados de la normatividad vigente.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: 28 de marzo de 2003

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 28/03/2003 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	EP 1277753	Thiazolidinedione derivative and its use as antidiabetic	19/04/2000

7. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

1) Respecto a la solicitud en estudio:

La reivindicación 1 se refiere a un procedimiento para la preparación de polimorfo maleato de rosiglitazona (compuesto 1) substancialmente libre de cualquier otra forma polimórfica, que comprende la cristalización de maleato de rosiglitazona en un solvente o mezcla de solventes con una constante dieléctrica tal que provea al compuesto 1 substancialmente libre de cualquier otra forma polimórfica.

2) Respecto al estado de la Técnica:

D1 enseña previamente el polimorfo de la sal del ácido maleico del compuesto 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]bencil]tiazolidin-2,4-diona (Ver resumen, reivindicación 1)

D1, además divulga, el proceso de preparación del polimorfo, mediante cristalización en alcohol denaturado.

3) Estado de la Técnica más cercano: D1

La solicitud se diferencia de D1, en que no se expresa la propiedad de la constante dieléctrica en el proceso de preparación del polimorfo.

El efecto técnico logrado es la obtención del polimorfo maleato de rosiglitazona, empleando solventes o mezcla de solventes, de acuerdo con su constante dieléctrica, con el fin que se encuentre libre de cualquier otro polimorfo de maleato de rosiglitazona.

El Problema Técnico Objetivo de esta solicitud, el cual es necesidad de proveer el polimorfo de maleato de rosiglitazona puro y su respectivo proceso de purificación, sería obtenido de forma evidente a partir de D1; pues a partir del conocimiento previo de su proceso de preparación con diferentes solventes tales como alcohol de naturado, el cual ya estaba previamente divulgado; se caracterizarían de tal forma por sus propiedades intrínsecas, tal como la constante dieléctrica; sin emplear por lo tanto habilidad inventiva.

No se evidencia el efecto técnico superior de la solicitud presentada, al emplear la constante dieléctrica de los solventes, en el proceso de preparación del polimorfo maleato de rosiglitazona frente a lo previamente divulgado en el estado de la técnica, pues el solicitante caracteriza los solventes previamente divulgados en los procesos de obtención de los polimorfos.

Para el experto en la materia, la solicitud se deriva de forma obvia del estado de la técnica, a partir del proceso de preparación de D1, ya que mediante el empleo de solventes como alcohol denaturado, implícitamente éste posee una constante dieléctrica; sin ser por lo tanto inesperado el uso de esta propiedad en el proceso de preparación.

De acuerdo cono anterior, las reivindicaciones 1 a 13 carecen de nivel inventivo.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	EP 1277753	1-13	Nivel Inventivo

9. Remisión de información:

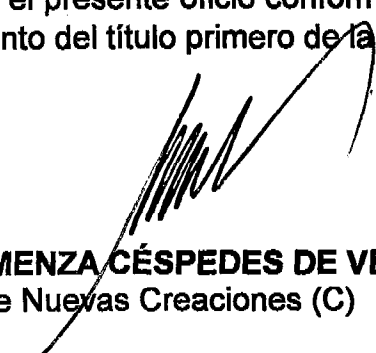
Los siguientes documentos fueron remitidos como información:
WO/2002/026737, WO/2000/064896, EP 1277753 y EP1284268; los cuales serán podrán ser tenidos en cuenta durante el estudio de patentabilidad. El documento EP 1277753 fue empleado en el presente estudio de patentabilidad.

La información anexada como Tecnología farmacéutica Volumen I, José Luis Vila Jato Editorial Síntesis. Madrid, páginas 44-50 y Giron D, Thermoquímica Acta 248-1-59, Elsevier Science B.V, 1995, Páginas 3 a 11; registra la fecha del año 1995, sin embargo,

147
no presenta las fechas de las correspondientes carátulas de los libros que las confirmen; por lo tanto no se pueden tener en cuenta en el estudio.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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 CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha **20 NOV. 2009**

CONCEPTO TÉCNICO No. 03014

EXAMINADOR TÉCNICO
Código No. 202070

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION.- 15518

Por la cual se niega una patente de invención

Rad. PCT/05-97262

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "PROCESO PARA LA PREPARACION DE UN POLIMERO DE MALEATO DE ROSIGLITAZONA", que corresponde a la solicitud internacional PCT/GB 2004/001306 de fecha 25 de marzo del 2004, fue radicada en esta Superintendencia el 26 de septiembre del 2005 bajo el número 05097262 00000000, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente"*.

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 141 a 147 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION¹⁴ 15518

Por la cual se niega una patente de invención

Rad. PCT/05-97262

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "PROCESO PARA LA PREPARACION DE UN POLIMERO DE MALEATO DE ROSIGLITAZONA", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Ian Raisbeck Llinas, en su calidad de apoderado de Glaxo Group Limited., o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **23 MAR. 2010**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


GUSTAVO VALBUENA QUIÑONES

Doctor
IAN RAISBECK LLINAS
Diagonal 34 N° 5 – 28.
Bogotá D.C.