111

OLARTERAISBECK
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref: Expediente No. 06-053.414

Solicitud de patente de invención *titulada*:

"MÉTODO PARA PREPARAR MULTIPARTÍCULAS FARMACÉUTICAS.".

Solicitante: PFIZER PRODUCTS INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 583

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de $210.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por $210.000 pesos

112

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 06-053414- -00003-0000

Dep: 2020 NUEVACREACION
Lve: 379 PASENACIONALII
Folios 2

RECIBO OFICIAL DE CAJA : 06 - 2,706
FECHA : ENERO 9 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ARTE BAJOREK	CONSIGNACION	BANCO DE BOGOTA	062754367	106773	09/01/2008	15,875,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
		TOTAL : $	210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

113

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-53414

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **583** DE

FECHA **18 DE DICIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **14 DE MARZO DE 2008**

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____

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PCT

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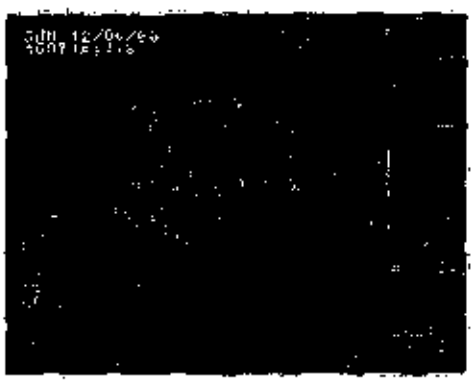
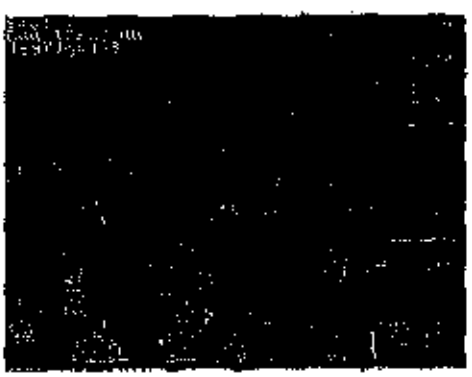
(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

[Continued on next page]

(54) Title: AMORPHOUS FLUTICASONE 2-FUROATE, PHARMACEUTICAL COMPOSITIONS THEREOF AND ITS CONVERSION TO THE CRYSTALLINE UNSOLVATED FORM

(57) Abstract: According to one aspect of the invention, there is provided a compound of formula (I) in the form of a substantially amorphous solid.





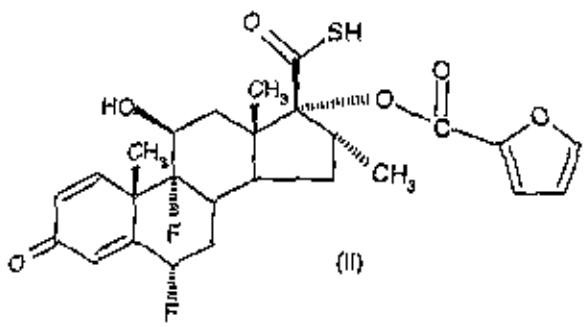
WO 03/066655 A1

more usually 0.5-10% especially 2-6% e.g. 3.5-4% w/w. The concentration that may be employed will be limited by the dissolution power of the solvent. Methylethylketone is preferred since it dissolves compound of formula (I) at a relatively high concentration which results in production advantages. Solubility of compound of formula (I) in the solvent may be enhanced by heating the solution. This may necessitate heating the appropriate parts of the apparatus (eg feed lines) to avoid unwanted precipitation of solids on cooling. The compound of formula (I) may be employed in non-solvated form or in the form of a solvate (e.g. with acetone). Preferably it is employed as the non-solvated Form 1 polymorph. Spray drying maybe performed, for example, using instruments supplied by Buchi or Niro. A pneumatic spray nozzle orifice of e.g. 0.04 inches (say 0.7-1.0 mm) is suitable, although alternate atomization methods such as rotary and pressure nozzles can be used. Solution flow rate may typically be in the range 1-100 ml/min, especially 15-30ml/min. The inlet temperature and flow rate combination should be suitable to evaporate the solvent completely to minimize the risk of solvent trapped in the particle expediting an amorphous to crystalline transition. Inlet temperatures can range from 50 – 250°C, typically 100 – 200°C.

As an aspect of the invention we also provide substantially amorphous particles of compound of formula (I) obtainable by performing an aforementioned process.

Compound of formula (I) may be prepared as follows:

A process for preparing a compound of formula (I) comprises alkylation of a thioacid of formula (II)



(II)

or a salt thereof.

polymorph) from compound of formula (I) as a substantially amorphous solid. Thus the process comprises (i) heating the substantially amorphous solid, particularly at a temperature of between 90°C and 160°C, until conversion is complete or (ii) contacting the substantially amorphous solid with vapours of a non-solvating solvent until conversion is complete. In step (i) if a temperature below 90°C is used the conversion may not take place, or may take place incompletely. At above 160°C chemical degradation may occur. The preferred temperature is between 90 and 100 °C, especially around 95°C. The length of time necessary to achieve conversion will depend on the temperature, however will typically be 1-3 hours e.g. 2 hours at 95 °C. Preferably the heating takes place in a controlled humidity environment. The time and temperature required to complete the amorphous to crystalline transition is dependent upon the process parameters used to produce the amorphous product and the resultant product thermal properties.

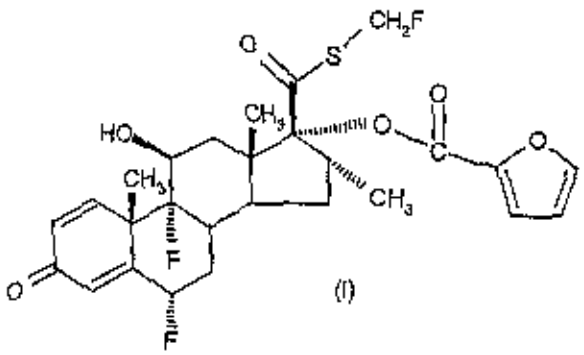
The temperature and time requirements for the conversion process can be decreased by the contacting the substantially amorphous solid with vapor of a non-solvating solvent (eg menthol, ethyl acetate, ethanol or methylisobutylketone (MIBK)).

Thus conversion to unsolvated polymorph can also be achieved without heating by contacting the compound of formula (I) as a substantially amorphous solid with vapours of a non-solvating solvent (eg menthol, ethyl acetate, ethanol or methylisobutylketone (MIBK) as per process (ii). The process normally results in generation of polymorph Form 1 (eg when ethyl acetate or MIBK are employed). However when ethanol is employed the process can result in generation of polymorph Form 2. Water is not suitable in this process; in fact compound of formula (I) in the form of a substantially amorphous solid appears to be quite stable in the presence of humidity. Process (ii) can normally be accelerated by heating eg up to around 70 °C. For example when vapours of menthol are employed in this process the conversion to unsolvated polymorph Form 1 takes 24-48 hours at room temperature however is accelerated to less than 1 hour on heating to 50 °C.

Agitation of the powder bed, by methods including, but not limited to vibrating, mixing or fluidization can be used in processes (i) and/or (ii) to minimize particle-particle contact and reduce the risk of bridging and subsequent particle size increase and loss of control during the surface crystallization process.

CLAIMS

1. A compound of formula (I)



(I)

in the form of a substantially amorphous solid.

2. A compound of formula (I) as defined in claim 1 in the form of substantially amorphous solid particles.

3. A compound of formula (I) in the form of substantially amorphous solid particles according to claim 2 wherein the particles are of controlled particle size suitable for inhalation.

4. A compound of formula (I) in the form of substantially amorphous solid particles according to claim 2 which particles are substantially spherical.

5. A pharmaceutical formulation suitable for topical administration to the lung or nose comprising a compound of formula (I) according to claim 2 optionally together with one or more physiologically acceptable diluents or carriers.

6. A pharmaceutical formulation according to claim 5 in the form of a dry powder composition which contains a powder base.

7. A pharmaceutical formulation according to claim 6 wherein the powder base is lactose.

8. A pharmaceutical formulation according to claim 6 in the form of a pressurised aerosol formulation

9. A pharmaceutical formulation according to claim 8 which contains a liquefied fluorocarbon or hydrogen-containing chlorofluorocarbon propellant gas, or mixture thereof.

10. A process for preparing a compound of formula (I) in the form of a substantially amorphous solid, as claimed in claim 1, which comprises spray drying a solution containing compound of formula (I).

11. A process according to claim 10 wherein the solvent is methylethylketone.

However, inhalation therapy is a particularly demanding dosing system and it involves its own set of unique design and performance problems. Amongst those problems is a concern over the accuracy and repeatability of dosing. One must try to ensure that the same amount of drug is administered each and every time. Moreover, unlike pills, capsules and creams, oral inhalation therapy must concern itself with not only the dosage form itself, but also a drug delivery device and the interaction between them. One has only to consider over-the-counter nasal sprays to understand this problem. When one squeezes a conventional squeeze bottle, it is difficult to apply the same amount of force each and every time. With even a slight difference in force, differences in the amount of drug administered can result. Even with somewhat more consistent pump style spray applicators, variations in dosing can occur. While such variation is usually not a problem when administering OTC nasal sprays, variation should be minimized where possible when administering prescription medications for such serious conditions as asthma. The dangers of over-medicating or under-medicating and the consequences of such unwanted deviation can be profound. The problem becomes even more complex when the size of the doses are as small as they often are in oral inhalation therapy.

To help mitigate these problems, companies such as Schering Corporation have developed complex and highly accurate inhaler systems for administering powdered medications such as those described in PCT International Publication No. WO 94/14492, which was published on July 7, 1994, the text of which is hereby incorporated by reference. Such inhaler systems were designed to meter out an exact dose of a powdered medication using a dosing hole of a specific size. The hole is completely filled with drug prior to administration and the entire contents of the dosing hole are then delivered to the patient through a nozzle. The dosing hole is then filled again for the next dose. These devices have been specifically designed to remove, as much as possible, human error and mechanically induced variability in dosing.

While such devices represent a significant advance in oral inhalation therapy, there are still some circumstances in which problems may

at least one solid binder. At least one of these two particles, the drug or the solid binder, includes as part thereof, a preselected amount of a convertible amorphous content which is sufficient to, upon crystallization thereof, allow for the formation of generally crystalline, agglomerates. The predetermined convertible amorphous content of the binder and/or the drug is capable of being converted to a crystalline form upon exposure to a preselected stimulus which includes, among other things, humidity.

The particles are then agglomerated while maintaining the preselected or predetermined amount of convertible amorphous content. After agglomeration is complete, the convertible amorphous content within the agglomerates is exposed to the preselected stimulus and is converted to a crystalline form. By "crystalline," it is understood that the agglomerates of the present invention can still contain some amorphous content, predominantly non-convertible amorphous phase with or without some amount of unconverted convertible amorphous content. The latter is to be minimized. Without wishing to be bound by any particular scientific theory, it is believed that the conversion of the convertible amorphous content creates crystalline bonds between the particles. These bonds are strong enough to preserve the integrity of the agglomerates during handling, storage and metering. However, they are soft enough to be overcome by commercially available inhalers so as to provide an acceptable fine particle fraction upon dosing.

It is an important aspect of the present invention that the agglomerates contain a certain content of convertible amorphous content during formation. "Convertible" means that the amorphous content, when exposed to certain predetermined or preselected stimuli, will convert from amorphous to crystalline form. This convertible amorphous content can be present as part of the drug, part of the solid binder, or both. The distribution of the amorphous content on the particles is generally unimportant so long as sufficient convertible amorphous content is present, preferably substantially homogeneously, throughout the system.

form, the binder must be stable, capable of supporting and maintaining an agglomerate and binding particles of therapeutically active agents such that same can be released as a fine particle fraction of particles. The binder must also impart to the crystalline agglomerate a desired range of properties including bulk density, strength, a free-flowing character, and storage stability.

Preferably, the convertible amorphous content of the solid binder, if indeed, it contains some or all of the convertible amorphous content of the agglomerate, will convert from its amorphous form to its crystalline form upon exposure to a preselected or predetermined stimulus such as atmospheric moisture in the form of humidity. However, materials which meet all of the foregoing criteria and will convert responsive to other preselected stimuli such as, for example, temperature, radiation, solvent vapor and the like may also be used. Preferred solid binders include polyhydroxy aldehydes, polyhydroxy ketones, and amino acids. Preferred polyhydroxy aldehydes and polyhydroxy ketones are hydrated and anhydrous saccharides including, without limitation, lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, mannitol, melezitose, starch, xylitol, mannitol, myoinositol, their derivatives, and the like.

Particularly preferred amino acids include glycine, alanine, betaine and lysine.

Where the drug is completely crystalline, or where it contains only non-convertible amorphous content, the solid binder must provide all of the amorphous content of the agglomerate system and vice versa. Neither the solid binder material, nor the drug need naturally have such an amorphous content, so long as such an amorphous content can be reversibly imparted thereto.

It is possible that the drug, the binder or both contains a certain percentage of amorphous content which is non-convertible or stable under the conditions of use and storage, as well as when the preselected stimuli is applied. This stable amorphous content is not part of the convertible amorphous content previously discussed. As is generally the case, this stable amorphous content has some role in interparticulate binding. However, it will

125

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado:
CARLOS REINALDO OLARTE GARCIA

ASUNTO:	Radicación No.	06 05 3414
	Trámite	011
	Evento	379
	Actuación	430
	Oficio	
	Folios	

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 comunica:

Documentos estudiados:

Descripción:	Folios 50 a 82 como se radicó inicialmente.
Reivindicaciones:	Folios 83 a 85 como se radicó inicialmente.
Prioridad:	US 60/527.316 (2003-12-04)

Objeto de la Invención

Titulo de la invención: "Método para preparar multipartículas farmacéuticas."

Problema Técnico Planteado: "Necesidad de un método para formar multipartículas que contengan fármaco en el que la conversión del activo a otra forma cristalina o amorfa se mantiene en niveles bajos aceptables."

Solución: "Proveer un mejor proceso fundido-solidificación para formar multipartículas que contienen el fármaco en forma cristalina en donde la forma cristalina de la droga incluye una especie volátil, es decir, la adición de la especie volátil ya sea a la mezcla fundida de fármaco y un vehículo o a una atmósfera en contacto con la mezcla fundida (i) durante la formación de la mezcla fundida, o (ii) durante su formación en gotas o (iii) tanto durante (i) como (ii)"

IPC: A61K 9/16 AC; A61K 31/7052

Análisis de la Solicitud de Patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Claridad y concisión: La reivindicación 1 reclama un proceso en el cual se emplea una temperatura T en el paso (a), lo cual le resta claridad a la reivindicación y permite que un técnico versado le de una apreciación subjetiva.

126

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación 04.12.2003 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO03/066655	*Amorphous fluticasone 2-furoate, pharmaceutical compositions thereof and its conversion to the crystalline unsolvated form*	14.08.2003
D2	WO1998/041193	*Preparation of powder agglomerates*	24.09.1998

Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: Un método de formación de multipartículas que comprende proporcionar un fármaco capaz de existir en forma cristalina que incluye una especie volátil que tiene una presión de vapor de al menos 0,01 atmósferas (1,013 KPa) a una temperatura de operación T seguido por las etapas siguientes:

- ✓ formar una mezcla fundida que comprende dicho fármaco y un vehículo a dicha temperatura T;
- ✓ formar gotitas de dicha mezcla fundida; y
- ✓ solidificar dichas gotitas en un medio de solidificación para formar multipartículas que comprenden dicho fármaco y dicho vehículo en el que dicha especie volátil se añade durante al menos una de las etapas (a); (b) y (c)."

D1 presenta un compuesto de fórmula I como sólido amorfo (folio 117) en su forma no solvatada o solvatada (página 13), y describe el secado por aspersión con un spray neumático de 0.7 mm, con un flujo de la solución que contiene el activo 15-30ml/min. Revela que $T_{entrada}$ y velocidad de flujo adecuadas para evaporar el disolvente y minimizar la transición cristalina. D1 revela la preparación de una forma no solvatada cristalina del activo que comprende:

- ✓ Calentamiento del solido amorfo, especialmente 90 – 160 °C, hasta la conversión completa y
- ✓ Contactar el sólido amorfo con vapores de un solvente no solvato hasta la conversión completa. (pej. mentol, acetato de etilo, metilbutilcetona)

Revela la temperatura preferida los 90 y 100 °C, durante 1 a 3 horas y bajo humedad controlada (página 16). D1 revela que el secado por aspersión que contiene el compuesto de formula I así como la preparación del activo como un solido amorfo seguido de el calentamiento y la exposición al solvente.

La solicitud se diferencia de D1 en la utilización de la mezcla fundida del activo y el vehículo.

El Efecto Técnico que logra la diferencia es proveer un proceso de fundido-solidificación que mantiene la forma cristalina deseada del fármaco en las multipartículas.

El Problema Técnico Objetivo de esta solicitud es proveer un método alternativo para formar multipartículas que contengan fármaco en el que la conversión del activo a otra forma cristalina o amorfa se mantiene en niveles bajos aceptables

D2 revela la formación de aglomerados (página 1) que contienen:

- ✓ un compuesto activo sólido en la forma de amorfo susceptible de ser convertido a la forma cristalina por exposición de un estímulo predeterminado como humedad y (página 7)

- ✓ y un aglutinante sólido que contiene una fracción sólida amorfa convertible de su forma amorfa a su forma cristalina a partir del estímulo preseleccionado (página 18).

Además, D2 revela que los materiales aglutinantes deben mostrar sensibilidad a estímulos como la temperatura, la radiación e incluso los vapores de solventes. Además presenta aglutinantes sólidos preferidos como polihidroxialdehidos y polihidroxicetonas y muestra el proceso de producción de aglomerados así:

- ✓ Agregar un primer material a un aglomerante, susceptible de ser convertido en forma cristalina con la exposición a factores determinados, en una magnitud tal que permite la formación de aglomerados,

- ✓ Aglomerar las partículas,

- ✓ Exponer el contenido amorfo convertible a los factores determinados con el fin de convertir dicho contenido amorfo convertible a una forma cristalina.

El experto en la materia habría sido motivado por las enseñanzas de D2 a incluir un aglomerante sensible a factores como la humedad o los vapores de solventes para cambiar de la forma amorfa a una sólida cristalina, a la materia presentada por D1 para así llegar a la materia reclamada por la presente solicitud.

Se concluye que las reivindicaciones 1 y sus dependientes no poseen nivel inventivo.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO03/066655	1-17	Nivel inventivo
D2	WO1998/041193	1-17	Nivel inventivo

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 60 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 CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

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

CONCEPTO TECNICO NUMERO: 4365	EXAMINADOR TÉCNICO Código:202092