

CASTELLANOS & CO LTDA

ABOGADOS

Calle 94 A No. 7 A-09

Bogotá, D.C. – COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-041742- -00008-0000

Fecha: 2011-12-27 15:07:15 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 449 RESPUESOPOSICI Folios: 10

Señor

Director de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Comercio, Desarrollo, Industria y Turismo

E. S. D.

Re.: Expediente No. 10.041.742

Solicitud de Patente de invención para: **"MÉTODOS DE TRATAMIENTO DE DESORDENES GASTROINTESTINALES INDEPENDIENTES DE LA INGESTA DE ALIMENTO"**

Solicitante: **TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.**

RESPUESTA A OPOSICION

MARGARITA CASTELLANOS ABONDANO, mayor de edad, identificada y domiciliada como aparece al pie de mi firma, atentamente me permito presentar respuesta al oficio No. 10889 notificado por fijación en lista el 14 de julio de 2011 correspondiente a la oposición presentada por **LABORATORIOS SYNTHESYS S.A.S.**, para el cual solicite prórroga con mi memorial de fecha 29 de septiembre de 2011, estando dentro del término legal en los siguientes términos:

- *El opositor argumenta en primer lugar que la presente solicitud de patente contempla materia referente al uso y a un método de tratamiento los cuales no son patentables de conformidad con la Decisión 486.*

Presento junto con este memorial un nuevo pliego reivindicatorio en donde se define una composición que comprende una primera y una segunda partícula sólida, las cuales comprenden dexlansoprazol como ingrediente activo, y un primer y segundo recubrimiento entérico, respectivamente. Así entonces, las modificaciones si son susceptibles de patentabilidad toda vez que definen un producto y solicito a su Despacho realizar el examen de patentabilidad sobre este nuevo pliego.

- El opositor considera que el documento US20060018964 (en adelante D1) publicado el 26 de enero de 2006 afecta la novedad de la presente solicitud toda vez que ya divulgaba un método para tratar enfermedades gastrointestinales en el cual se administra a un paciente

una cantidad efectiva de una forma de dosificación de un inhibidor de bomba de protones y en donde la composición farmacéutica puede administrarse independientemente de la ingesta de alimentos.

El solicitante manifiesta que el documento US 2006/0018964 no enseña el empleo de dexlansoprazol. Como se indica en el párrafo [0019] de este documento, se encontró sorprendentemente que la presencia de xilitol y/o maltitol, en su forma directamente compresible y en una muy pequeña cantidad, mejora la capacidad de la mezcla de excipientes para comprimirse y retener las propiedades gastro-protectoras proporcionadas por el polímero entérico. En consecuencia, el documento que cita el opositor no revela todas y cada una de las características técnicas de la invención reivindicada y no puede afectar su novedad.

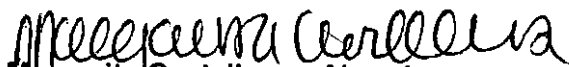
Adicionalmente, la publicación US2006/0018964 no enseña una composición que puede administrarse independientemente de la ingesta de alimentos. Contrario a lo reportado por el señor opositor, el resumen del documento citado no hace referencia alguna a la ingesta de comida, únicamente, se refiere a tabletas que se desintegran sin necesidad de masticarlas. (Adjunto copia del resumen para su fácil referencia)

En este orden de ideas, D1 no constituye un documento de particular relevancia para el estudio de patentabilidad de la solicitud toda vez que pretende resolver un problema distinto. Como se indica en el párrafo [0005], la invención de D1 esta dirigida a proteger las sustancias activas de la descomposición por ácido gástrico mediante un recubrimiento entérico para diferentes sustancias farmacéuticamente activas. Además se afirma en D1 que la invención resuelve el problema técnico existente en cuanto a la resistencia mecánica de los recubrimientos a la compresión mediante el empleo de excipientes como xilitol y/o maltitol que evita la aplicación de fuerzas de compresión en la formación de las tabletas.

Por su parte, la presente invención proporciona una composición útil para el tratamiento de enfermedades gastrointestinales que puede ser administrada a un paciente sin condicionamiento con respecto a la ingesta de comida. Así, como se indica en el texto de esta invención, los medicamentos existentes en el mercado requieren ser administrados antes de comer y los pacientes no pueden tomarlos en el momento que ellos los necesitan sino que tienen que recordar por lo menos una hora antes de comer que necesitan tomar el medicamento. Entonces, la invención busca solucionar este problema y propone una composición farmacéutica que puede administrarse sin importar que la persona haya comido.

Así entonces, D1 constituye un documento del campo técnico en general pero que no podría afectar la novedad de la composición de la invención toda vez que corresponde a productos distintos que no comprenden los mismos elementos técnicos. Dichas deferencias obedecen precisamente a que están dirigidos a resolver problemas técnicos diferentes.

Solicito entonces a ese Despacho declarar infundada la oposición que presenta LABORATORIOS SYNTHESYS S.A.S por cuanto el documento citado no anticipa la invención reivindicada por mi representada, y continuar el estudio de patentabilidad sobre la base de arte previo relacionado con la invención.



Margarita Castellanos Abondano

C.C. No. **39.779.654** de Usaquén

T.P.A. No. **70.819** del Consejo Superior de la Judicatura

Calle 94 A No. 7 A-09 – Bogotá, D.C.

Teléfono: 756 0770

Bogotá, D.C. **27 DIC. 2011**
MCA/

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

①

SOLICITUD DE:

☐ Corrección de Error Material

☒ Modificación a una solicitud

②

SOLICITANTE

Nombre: **TAKEDA PHARMACEUTICALS
NORTH AMERICA, INC**
Dirección: **One Takeda Parkway
Deerfield, IL 60015
ESTADOS UNIDOS DE AMERICA**
Nacionalidad o Domicilio: **Deerfield, IL
ESTADOS UNIDOS DE AMERICA**
Lugar de Constitución **ESTADOS UNIDOS
DE AMERICA**

Teléfono: _____ Fax: _____
E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

③

REPRESENTANTE
O APODERADO

Nombre: **MARGARITA CASTELLANOS A.**
Dirección: **CALLE 94A No. 7A-09**
Teléfono: **756 07 70** Fax: **755 01 58**
E-mail: **info@castellanosyco.com**

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número **39'779.654** TPA **70.819**

④

Número de Expediente:

10.041.742

⑤

Descripción de la corrección o modificación solicitada:

Presento pliego reivindicatorio modificado para el estudio de patentabilidad de ésta solicitud.

⑥

Comprobante de pago No.

11-113534

Fecha

22/11/2011

⑦

Anexos:

☒ Comprobante de pago de la tasa.

☐ Poderes si fuere el caso, junto con la sustitución de los mismos a mi favor.

☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas

☒ Nuevo capítulo reivindicatorio

⑧

NOMBRE **MARGARITA CASTELLANOS A.**

FIRMA

Margarita Castellanos A.
CC 39'779.654 Usaquén - TPA 70.819 CSJ

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página - MCA/zca-P1933

27 DIC. 2011

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

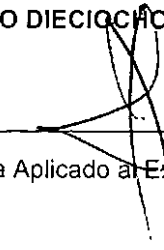
 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 11 - 113534
		Bogotá D.C., Noviembre 22 de 2011 - 13:56:25

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	387647691	22/11/2011	9.262.000.00

*** Conceptos Pagados ***			
CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO Vr. CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD INDUSTRIAL	99 OTROS SERVCIOS ADMINISTRATIVOS	118.000.00 118.000.00
			\$118.000.00
=====			

SON: **CIENTO DIECIOCHO MIL PESOS MONEDA CORRIENTE**

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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REIVINDICACIONES MODIFICADAS

1. Una composición farmacéutica que comprende

(a) una primera partícula sólida, donde dicha primera partícula sólida comprende dexlansoprazol y un primer recubrimiento entérico, donde el primer recubrimiento entérico libera el agente activo de la partícula sólida a un pH de cerca de 5.0 a cerca de 5.5., y

(b) una segunda partícula sólida, donde dicha segunda partícula sólida comprende dexlansoprazol y un segundo recubrimiento entérico, donde el segundo recubrimiento entérico libera el agente activo de la partícula sólida a un pH de cerca de 6.2 a cerca de 6.8;

En donde una cantidad terapéuticamente efectiva de dicha composición farmacéutica puede administrarse a un paciente independientemente de la ingesta de alimento.

2. Una composición farmacéutica que comprende

(a) una primera partícula sólida, donde dicha primera partícula sólida comprende dexlansoprazol y un primer recubrimiento entérico, donde el primer recubrimiento entérico libera el agente activo de la partícula sólida a un pH de cerca de 5.0 a cerca de 5.5., y

(b) una segunda partícula sólida, donde dicha segunda partícula sólida comprende dexlansoprazol y un segundo recubrimiento entérico, donde el segundo recubrimiento entérico libera el agente activo de la partícula sólida a un pH de cerca de 6.2 a cerca de 6.8;

En donde la primera partícula sólida comprende desde 15% a 50% en peso de la composición farmacéutica y la segunda partícula sólida comprende desde 50% a 85% en peso de la composición farmacéutica; y

Además donde una cantidad terapéuticamente efectiva de dicha composición farmacéutica puede administrarse a un paciente independientemente de la ingesta de alimento.

3. La composición de las reivindicaciones 1 o 2, donde el primer recubrimiento entérico tiene un pH de 5.5.

4. La composición de las reivindicación 3, en donde el primer recubrimiento entérico comprende una dispersión de copolímero de ácido metacrílico.

5. La composición de las reivindicaciones 1 o 2, donde el segundo recubrimiento entérico tiene un pH de 6.75.

6. La composición de las reivindicaciones 1 o 2, donde el segundo recubrimiento entérico comprende una mezcla de un copolímero Tipo B metacrílico y un copolímero Tipo A metacrílico en una relación de 3:1.
7. La composición de las reivindicaciones 1 o 2, donde la primera partícula sólida comprende una capa protectora entre el agente activo y el primer recubrimiento entérico.
8. La composición de las reivindicaciones 1 o 2, donde la segunda partícula sólida comprende una capa protectora entre el agente activo y el segundo recubrimiento entérico.
9. El método de las reivindicaciones 7 u 8, donde la capa protectora es sacarosa, hipromelosa, un recubrimiento no entérico o cualquier combinación de estos.
10. La composición de la reivindicación 9, donde el recubrimiento no entérico es hidroxipropilcelulosa.
11. La composición de las reivindicaciones 1 o 2,, donde la primera partícula sólida comprende 25% de la composición farmacéutica y la segunda partícula sólida comprende 75% de la composición farmacéutica.
12. La composición de las reivindicaciones 1 o 2, donde la primera partícula sólida es un gránulo.
13. La composición de las reivindicaciones 1 o 2,, donde la segunda partícula sólida es un gránulo.
14. La composición de las reivindicaciones 1 o 2, donde la composición farmacéutica es una tableta o una cápsula.



US 20060018964A1

(19) **United States**

(12) **Patent Application Publication**

Combessis et al.

(10) **Pub. No.: US 2006/0018964 A1**

(43) **Pub. Date: Jan. 26, 2006**

(54) **PHARMACEUTICAL FORMULATION AND
PROCESS FOR ITS PREPARATION**

Publication Classification

(75) **Inventors:** Danielle Combessis, Montpellier (FR);
David Corvaisier, Biot (FR);
Alexandre Gil, Moguins (FR);
Emmanuel Guerin, Colombes (FR)

(51) **Int. Cl.**
A61K 9/22 (2006.01)
(52) **U.S. Cl.** 424/468

(57) **ABSTRACT**
The present invention relates to a multiparticulate tablet with improved gastro-protection comprising at least a pharmaceutically active substance in the form of enteric coated particles, and a mixture of tableting excipients, wherein the said mixture of excipients comprising xylitol and/or maltitol, each in a directly compressible form, a disintegrating agent, a lubricant and at least one other diluent and the ratio of a) the xylitol and/or the maltitol to b) the other diluent(s) is less than 5/95 (weight/weight) and the result of the "test of integrity of the film" is greater than 95%, preferably greater than 97% and more preferably still greater than 99% and the result of the "release test" is greater than 90%, preferably greater than 95%. According to one embodiment of the invention, the active substance is omeprazole or esomeprazole. According to another embodiment the tablet is a disintegratable tablet, which disintegrate in the mouth with or without chewing. The invention also comprises a process for preparing the claim tablet and its use in medicine.

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(73) **Assignee:** AstraZeneca AB

(21) **Appl. No.:** 11/181,170

(22) **Filed:** Jul. 13, 2005

(30) **Foreign Application Priority Data**
Jul. 26, 2004 (EP) 04291900.1

PHARMACEUTICAL FORMULATION AND PROCESS FOR ITS PREPARATION

FIELD OF THE INVENTION

[0001] The present invention relates to a multiparticulate tablet comprising a multiple of small enteric coated pellets or particles of a pharmaceutically active substance. According to one aspect of the invention, the active substance is an acid labile proton pump inhibitor compound. According to another aspect the multiparticulate tablet comprising a pharmaceutically active substance is an orally disintegratable tablet, which disintegrate in the mouth. The present invention also relates to processes for the preparation of the said tablets and their use in medicine.

BACKGROUND OF THE INVENTION

[0002] Pharmaceutically active substances have different physicochemical and biopharmaceutical characteristics, which in some cases require that the release of the substance is target so as to obtain optimal absorption of the active substance in the body, for instance to avoid possible decomposition of the active substance in the acidic stomach. This is specifically true for substances that are sensitive to gastric acidity or the substance need to be released as close as possible to its site of absorption and/or action.

[0003] In the present patent application, the terms "enteric polymer", "enteric coating", "gastro-resistant polymer" and "gastro-resistant coating" will be used interchangeable.

[0004] The use of an enteric or gastro-resistant polymer allows the Formulator to formulate the active substance so that it remains intact during its passage and/or its time of residence in the acidic gastric juice. The passage of the stomach, which may take approximately up to two hours, includes presence in a medium with a pH of between approximately 1 and 3. Once in the small intestine, which comprises of the duodenum, the jejunum and the ileum, the enteric coating will rapidly dissolve. The small intestine comprises a medium with a pH of greater than 4.5 and which gradually increases up to a pH of approximately 7.2 in its distal part.

[0005] Thus, active substances, which are acid labile, will be decomposed by the acidic gastric juice and they require gastro-protection for oral administration. There are some active substances that might be acid stable but irritating the gastric mucosa and therefore benefit from a protective layer. Thus, there might be a need for gastro-protection, i.e. an enteric coating, for different types of pharmaceutically active substance.

[0006] For oral administration, it is particularly advantageous to formulate such active substances to multiple unit dosage forms. The active substance is formulated to small particles, such as pellets, micro tablets, spheroids or granules, preferably small spherical particles, see for instance EP-A-247 983, which are covered with a subcoating layer and an outer enteric coating.

[0007] The small particles can be composed according to different principles, such as a seed (for instance a sugar sphere) layered with the active substance and/or pharmaceutically acceptable constituents or the active substance is mixed with pharmaceutical acceptable constituents and the

particles are produced by extrusion/spheronisation, balling or compression utilizing suitable process equipment.

[0008] The small particles, i.e. a core material comprising the active substance, will be coated with a subcoating layer and an external layer composed of at least one enteric polymer.

[0009] The coated particles are subsequently placed in capsules, such as hard gelatine capsules. Alternatively, cellulose capsules for instance capsules of hydroxyl propyl methylcellulose can be used.

[0010] In alternatively multiple unit dosage forms, the coated particles are compressed to a tablet after being mixed with pharmaceutically acceptable tablet excipients. When preparing multiple unit tablets, the application of compression forces to the tablet mixture comprising coated particles present a problem with respect to the strength of the coating and specifically the requirement to maintain the gastro-resistance and the integrity of the tablet and of the enteric coated units after tableting. WO 96/01624 discloses a multiple unit tablet comprising gastro-resistant micro-granules of a proton pump inhibitor compound wherein the enteric coating maintain the gastro-resistance and withstand the compression forces during tableting.

[0011] It has been shown that the film-forming agents generally used to coat particles cannot under normal conditions absorb the mechanical stresses applied during tableting (International Journal of Pharmaceutics, No. 143, 13-23, 1996). Films composed of only enteric polymers or copolymers have very mediocre mechanical properties, such that they do not withstand tableting. The application of these compression forces can result in the appearance of cracks in the enteric coating film or by the splitting thereof, resulting in the partial or complete loss of the properties of the film coating.

[0012] The prior art provides solutions such as for example modifying the composition of the enteric coating films, so as to substantially improve its mechanical characteristics with regard to tableting properties, i.e. to withstand the application of compression forces. Improvements in gastro-resistance and less film damage can also be achieved by using excipients that deform plastically during tableting.

[0013] The document "Drugs made in Germany", 37, No. 2 (1994), p. 53, teaches that it is possible to combine Eudragit® L30D and Eudragit® NE30D to produce multiparticulate tablets comprising the said enteric coated particles. However, this approach does not work for all active principles, such as coating of acidic sensible compounds.

[0014] WO 02/19991 (Röhm) relates to a multiparticulate tablet and gastro-resistant micro-granules, wherein the said micro-granules comprise an enteric coating of a methacrylic acid copolymer and propylene glycol. The proportion of the said granules in the tablets is between 35% and 90%, preferably 40% to 70%, by weight, with respect to the total weight of the tablet, the remainder being a binder.

[0015] Alternative solutions consist of diluting/mixing the enteric coated particles with auxiliary substances, which substances can absorb the physical stresses during tableting. This solution often requires a lengthy formulation operation and is not suited to all types of tablets, such as water-

dispersible tablets, or tablets, which disintegrate in the mouth, with or without chewing.

[0016] Orally disintegratable tablets, which disintegrate in the mouth, are disclosed for instance in EP 548356, EP 1003484, EP 1126821, EP 1156786, WO 03/007917, WO 98/53798 and WO 00/78292.

[0017] EP 1003484 describes a composition of an active ingredient with a taste-masking coating and tablet excipients comprising at least one disintegrating agent and at least one soluble diluent agent with binding properties. WO 98/53798 describes a solid preparation comprising a pharmaceutically active ingredient, one or more water-soluble sugar and low-substituted hydroxypropylcellulose having hydroxyl group contents of 7.0 to 9.9% by weight. WO 00/78292 describes quickly disintegrating solid preparations containing an active ingredient, D-mannitol having an average particle size of 30 μm to 300 μm , a disintegrating agent and celluloses.

OUTLINE OF THE INVENTION

[0018] It is now surprisingly been found that it is possible, by adding a small amount of a specific diluent to the mixture of tableting excipients, to prepare a multiparticulate tablet comprising a pharmaceutically active substance such as for instance a proton pump inhibitor, exemplified with omeprazole and esomeprazole, in the form of enteric coated particles without the application of tableting forces, which may detrimentally affect the integrity of the coated particles. The multiparticulate tablet of the present invention exhibits an improved gastro-resistance.

[0019] Surprisingly and unexpectedly, it has been found that the presence of xylitol and/or of maltitol, in their directly compressible form and in a very small amount, makes it possible to improve the tableting ability of the mixture of tablet's excipients to be tableted and to retain the gastro-protective properties provided by the enteric polymer.

[0020] It has been shown that once disintegrated, the coated particles from the multiparticulate tablet of the invention are retained independently and intact. The release profiles obtained from the tablet comprising the enteric coated particles of the pharmaceutically active substance such as a proton pump inhibitor is virtually the same as the release profile from the coated particles as such and before the compression to a tablet.

[0021] The presence of xylitol and/or of maltitol, in their directly compressible form and in a very small amount, surprisingly makes it possible to retain organoleptic characteristics and a rate of disintegration which are equivalent to those of tablets which do not comprise these directly compressible sugars. These characteristics are specifically important and essential for water-dispersible tablets and orally disintegratable tablets, which disintegrate in the mouth, with or without chewing of the tablets.

[0022] The invention thus relates to a multiparticulate tablet with an improved gastro-protection comprising at least a pharmaceutically active substance in the form of enteric coated particles, and a mixture of tableting excipients, the said mixture of excipients comprising xylitol and/or maltitol, each in a directly compressible form, a disintegrating agent, a lubricant and at least one other diluent. The ratio of a) the xylitol and/or the maltitol to b) the other diluent(s)

is less than 5/95 (weight/weight). The result of the "test of integrity of the film" is greater than 95%, preferably greater than 97% and more preferably still greater than 99% and the result of the "release test" is greater than 90%, preferably greater than 95%.

[0023] According to one aspect of the invention, the multiparticulate tablet is an orodispersible tablet tablets which are able to disintegrate or dissolve in the buccal cavity, without mastication, upon contact with saliva, in less than 60 seconds and preferably less than 40 seconds, forming a particle suspension that is easy to swallow, said tablet comprising at least a pharmaceutically active substance in the form of enteric coated particles, and a mixture of tableting excipients at least comprising xylitol and/or maltitol, each in a directly compressible form, a disintegrating agent, a lubricant and at least one other diluent, the ratio of a) the xylitol and/or the maltitol to b) the other diluent(s) is less than 5/95 (weight/weight), and optionally a swelling agent, an antistatic agent, a permeabilising agent, sweeteners, flavoring agents and colors.

[0024] The disintegration time corresponds to the time between the moment when the tablet is placed on the tongue and the moment that the suspension resulting from the disintegration or dissolution of the tablet is swallowed.

[0025] According to another aspect of the invention the pharmaceutically active substance is a proton pump inhibitor. Thus, the invention relates to a multiparticulate tablet with an improved gastro-protection comprising at least one proton pump inhibitor, such as omeprazole or esomeprazole, in the form of enteric coated particles, and a mixture of tableting excipients, the said mixture of excipients comprising xylitol and/or maltitol, each in a directly compressible form, a disintegrating agent, a lubricant and at least one other diluent. The ratio of a) the xylitol and/or the maltitol to b) the other diluent(s) is less than 5/95 (weight/weight). The result of the "test of integrity of the film" is greater than 95%, preferably greater than 97% and more preferably still greater than 99% and the result of the "release test" is greater than 90%, preferably greater than 95%.

[0026] The "test of integrity of the film" and the "release test" make it possible to characterize the gastro-resistance of multiparticulate tablets.

[0027] These tests are carried out in the following way:

"Test of Integrity of the Film":

[0028] The enteric pharmaceutical dosage form (according to the present invention, a multiparticulate tablet) is placed for 120 minutes in a dissolution medium with a pH of 1.2. After this period of time the coated active particles are collected.

[0029] The amount of active substance remaining within the enteric coating is then assayed, which makes it possible to directly assess the integrity of the insoluble enteric coating film at pH 1.2. Any amount of active substance released into the acidic medium, in the event of a detrimental change of the enteric coating, will be decomposed itself by the medium.

[0030] The result is expressed as percentage by weight with respect to the total starting amount of the active substance.