

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE:

Eliana I. Moreno B

FIRMA:

Eliana I. Moreno B

C.C. 51.975.664

TP. 83823

Señor Jefe,

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 10 041742

Asunto : Oposición a la solicitud de patente de Invención titulada
"MÉTODOS DE TRATAMIENTO DE DESORDENES
GASTROINTESTINALES INDEPENDIENTES DE LA
INGESTA DE ALIMENTO"

Solicitante : TAKEDA PHARMACEUTICALS NORTH AMERICA,
INC.

Opositora : LABORATORIOS SYNTHESYS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial

N° 626 del 22 de marzo de 2011

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *83823* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESYS S.A.S** Conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "MÉTODOS DE TRATAMIENTO DE DESORDENES GASTROINTESTINALES INDEPENDIENTES DE LA INGESTA DE

ALIMENTO”, cuyos titulares son **TAKEDA PHARMACEUTICALS NORTH AMERICA, INC**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular inhibidores de la bomba de protones. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 12 de abril de 2010 reivindicando prioridad bajo la solicitud US20070998754P del 2007-10-12; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 626 del 22 de marzo de 2011, cuya publicación internacional corresponde a la WO 2009049160 del 2009-04-16.

2.2. La solicitud colombiana 10 041.742 objeto de la presente oposición se refiere a un método de tratamiento de un desorden gastrointestinal en un paciente en necesidad de éste, el método comprende las etapas de: administrar a dicho paciente una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de una forma de dosificación que incluye un inhibidor de la bomba de protones, en donde dicha composición farmacéutica se puede administrar a un paciente independiente de la ingesta de alimento.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y método terapéutico y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Sólo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento no sería patentable.

2.4. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*, tenemos que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

- D1: US20060018964 publicada el 26 de enero de 2006.

2.5. Ahora bien, el documento D1, se refiere a una tableta multiparticulada que comprende una sustancia farmacéutica activa en forma de partículas con cubierta entérica, y una mezcla de excipientes comprimidos, en donde la mezcla de excipientes comprende: un primer diluyente seleccionado del grupo que consiste de xilitol, maltitol y mezclas de los mismos, en donde el primer diluyente está en forma directamente compresible; un agente de desintegración, un lubricante, y por lo menos un siguiente diluyente. Particularmente, D1 describe un método para tratar una enfermedad gastrointestinal en un paciente que necesita tratamiento que comprende las etapas de: administrar a dicho paciente una composición farmacéutica que comprende una cantidad efectiva de una forma de dosificación de un inhibidor de bomba de protones en donde la composición farmacéutica es capaz de ser administrado a un paciente independiente de la ingesta de alimentos (resumen, párrafo [0001]). Igualmente, D1 describe un método para tratar una enfermedad gastrointestinal en un paciente en necesidad de tratamiento, cuyas etapas comprenden: administrar a dicho paciente una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de: (a) una primera partícula sólida, que comprende un agente activo y una primera capa entérica (párrafos [0003] - [0005]), excepto en donde la primera cubierta de recubrimiento entérico libera el agente activo de la partícula sólida a un pH de aproximadamente 5,0 a 5,5; (b) una segunda partícula sólida, que comprende un agente activo y un segundo recubrimiento entérico (párrafos [0003] - [0005]), en donde dichas primeras partículas sólidas se componen de cerca de 15% a 50% en peso de la composición farmacéutica y la segunda partícula sólida abarca de cerca de 50% a 85% en peso de la composición farmacéutica (párrafo [0072], [0074], [0080]). Según D1, la composición farmacéutica es capaz de ser administrada a un paciente

independiente de la ingesta de alimentos (ver resumen). Así las cosas, además de comprender el uso y método terapéutico que no es objeto de protección en Colombia, tampoco lo revelado es novedoso a la luz de la anterioridad D1. En consecuencia, la presente no comprende el requisito de novedad.

2.6. Por lo tanto, de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 10 041.742 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARENCIA DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 12 de octubre de 2007 ya era conocido, pues como se demostró, eran parte del arte anterior con base en los documentos D1, un método de tratamiento de un desorden gastrointestinal en un paciente en necesidad de éste, el método comprende las etapas de: administrar a dicho paciente una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de una forma de dosificación que incluye un inhibidor de la bomba de protones; sobre lo cual busca protección en el capítulo reivindicatorio.

2.7.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la*

tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial". La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada **"MÉTODOS DE TRATAMIENTO DE DESORDENES GASTROINTESTINALES INDEPENDIENTES DE LA INGESTA DE ALIMENTO**, cuyos titulares son **TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 626 del 22 de marzo de 2011.

3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: **US20060018964** publicada el 26 de enero de 2006.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

- 5.1. En las demás normas concordantes.
- 5.2. Poder para actuar en el presente.
- 5.3. Documento que acredita al representante legal de **LABORATORIOS SYNTHESYS S.A.S.**
- 5.4. Recibo de caja del respectivo pago de tasa.
- 5.5. Copias de los documentos:

D1: **US20060018964** publicada el 26 de enero de 2006.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

PODER ESPECIAL

Yo, **ORLANDO MUÑOZ MARTINEZ**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 10 041.742, titulada "**MÉTODOS DE TRATAMIENTO DE DESORDENES GASTROINTESTINALES INDEPENDIENTES DE LA INGESTA DE ALIMENTO**", cuyo titular **TAKEDA PHARMACEUTICALS NORTH AMERICA, INC** publicada en la gaceta No. 626 del 22 de marzo de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Bogotá (Colombia) a los 09 días del mes de junio de 2011.

LABORATORIOS SYNTHESIS S.A.S.



C.C. 8.317.044 de Medellín

NIT: 860.000.760-1

Representante Legal

Acepto:



ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



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DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo
de Bogotá: *Diego*
Morales
quien exhibió la C.C. *8317044*
Expedida en *Medellin* y
declaró que la firma y huella que
aparecen en el presente documento
son suyas y que el contenido del mismo
es cierto.

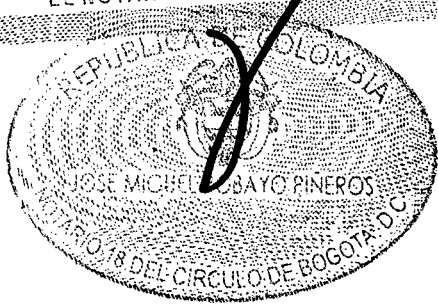
13 JUN 2011
BOGOTA, D.C.

FIRMA
Diego Morales
EL NOTARIO



HUELLA DEL
INDICE DERECHO

NOTARIA DIECIOCHO DEL
CIRCULO DE BOGOTA D.C.
LA HUELLA SE AUTENTICA POR
SOLICITUD DEL INTERESADO



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0050502

Bogotá D.C., Mayo 26 de 2011 - 10:25:46

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.

NI 860.000.760

***** Soporte del Pago *****

TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	435179146	25/05/2011	2.128.000.00

***** Conceptos Pagados *****

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	304.000.00	304.000.00
				\$304.000.00
			=====	

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



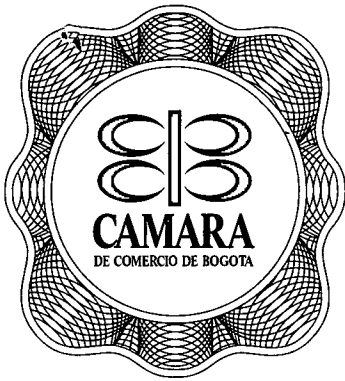
No. 10-041742- -00005-0000

Fecha: 2011-06-16 16:06:44 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 29

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

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Mayo 26 de 2011 - 10:25:47



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CAMARA DE COMERCIO DE BOGOTA

SEDE PALOQUEMAO

10 DE JUNIO DE 2011

HORA 09:58:10

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PAGINA: 1 de 5

* * * * *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S

N.I.T. : 860000760-1

DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL DE NOTIFICACION JUDICIAL : synthe@synthesis.com.co

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL : synthe@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950, BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA - CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LABORATORIOS BALBAG".

CERTIFICA:

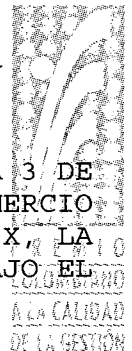
QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE COMERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LIBRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE: "LABORATORIOS --- BALBAG" POR EL DE "LABORATORIO SYNTHESIS" E INTRODUJO OTRAS REFORMAS.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. - DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.



CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SNTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SNTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

CERTIFICA:

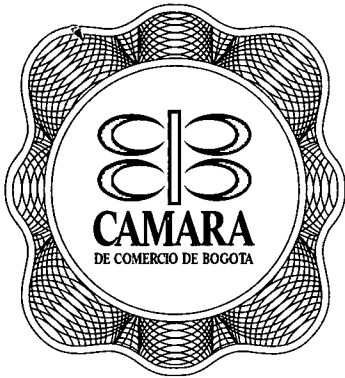
QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.

FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956 8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958 8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961 8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967 6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967 6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967 8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968 6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970 6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970 6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971 3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984 11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985 11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985 1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986 1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986 1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987 1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990 1 BTA.	3- IX -1.990 NO.303.579
9244	23-XII- 1991 1 STAFE.BTA.	8-I -1.992 NO.351.255
8145	15- X - 1992 1 STAFE.BTA.	16- X-1.992 NO.382.488
1374	26- III-1993 1 STAFE.BTA.	19- III-1993 NO.399972
3120	01-VI-1.995 1A.STAFE BTA	23-VI- 1.995 NO.498.060
5435	17-IX-1.996 1A.STAFE BTA	30-IX- 1.996 NO.556.909
5435	17-IX-1.996 1A.STAFE BTA	01- X- 1.996 NO.557.146
5435	17-IX-1.996 1A.STAFE BTA	02- X- 1.996 NO.557.301
5942	7-X -1.996 1A.STAFE BTA	11- X- 1.996 NO.558.222
6305	24-X--1.996 1A.STAFE BTA	07-XI--1.996 NO.561.207
6929	25-XI-1.996 1A.STAFE BTA	12-XII-1.996 NO.565.961
787	19-II-1.997 1A.STAFE BTA	25-II -1.997 NO.575.141



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CAMARA DE COMERCIO DE BOGOTA

SEDE PALOQUEMAO

10 DE JUNIO DE 2011

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PAGINA: 2 de 5

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1024

28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO. INSC.
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0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANTE Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS:

A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER

OPERACIÓN COMERCIAL O CIVIL, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER

ALA CALIDAD
DE LA GESTIÓN

14

~~CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES.~~

CERTIFICA:

CAPITAL:

**** CAPITAL AUTORIZADO ****

VALOR : \$20,000,000,000.00
NO. DE ACCIONES : 20,000,000.00
VALOR NOMINAL : \$1,000.00

**** CAPITAL SUSCRITO ****

VALOR : \$17,633,742,000.00
NO. DE ACCIONES : 17,633,742.00
VALOR NOMINAL : \$1,000.00

**** CAPITAL PAGADO ****

VALOR : \$17,633,742,000.00
NO. DE ACCIONES : 17,633,742.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: GERENCIA LA CUAL SERÁ ASUMIDA POR UN GERENTE Y UN SUBGERENTE QUIENES TENDRÁN REPRESENTACIÓN LEGAL DE LA SOCIEDAD.

CERTIFICA:

**** NOMBRAMIENTOS ****

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO

C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

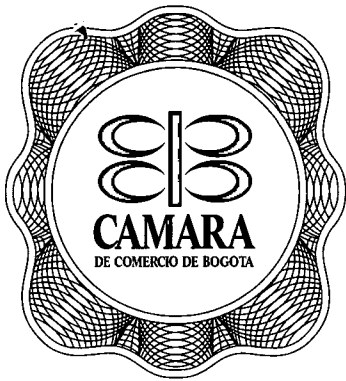
SUBGERENTE

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA



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CAMARA DE COMERCIO DE BOGOTA

SEDE PALOQUEMAO

10 DE JUNIO DE 2011

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PAGINA: 3 de 5

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DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

CERTIFICA:

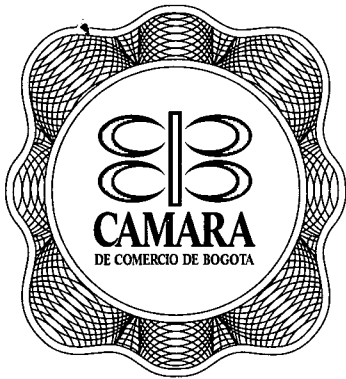
QUE POR ESCRITURA PUBLICA NO. 654 DE LA NOTARIA 01 DE BOGOTA D.C., DEL 20 DE FEBRERO DE 2009, INSCRITA EL 02 DE MARZO DE 2009 BAJO EL NO. 15209 DEL LIBRO V, COMPARECIO ORLANDO MUÑOZ MARTINEZ IDENTIFICADO CON CEDULA DE CIUDADANIA NO. 8.317.044 EN SU CALIDAD DE DELEGADO GENERAL SUPLENTE DEL SOCIO GESTOR LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL SEÑOR ANDRES FERNANDO MOLLAJOLI CENTURION, IDENTIFICADO CON CÉDULA DE EXTRANJERÍA NO. 351.283 QUE EN NOMBRE DE LA SOCIEDAD QUE REPRESENTO, ACTUÉ CON LAS MÁS AMPLIAS FACULTADES EN LA REPÚBLICA DE COLOMBIA, EN LOS SIGUIENTES ASUNTOS 1. PARTICIPAR EN CALIDAD DE SOCIO, ACCIONISTA O EMPRESARIO EN PERSONAS JURÍDICAS COLOMBIANAS, CONSTITUIDAS O POR CONSTITUIRSE, EN EL PORCENTAJE QUE LA APODERADA AQUÍ NOMBRADA ESTIME CONVENIENTE A NUESTROS INTERESES, CON FACULTAD PARA ENTREGAR LAS SUMAS CORRESPONDIENTES AL PAGO DEL MISMO; 2. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS; 3. REPRESENTAR A LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., EN LAS REUNIONES ASAMBLEA GENERAL O JUNTAS EN LAS CUALES TENGA INTERÉS; 4. EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRÉSTAMOS DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS, OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, Y NEGOCIAR EN GENERAL TÍTULOS VALORES Y RECIBIRLOS EN PAGO; 5. CELEBRAR ASÍ MISMO OPERACIONES RELACIONADAS CON LA PROTECCIÓN DE SUS BIENES, NEGOCIOS Y O PERSONAS A SU SERVICIO; 6. CELEBRAR CONTRATOS DE CUENTAS

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ALA CALIDAD
DE LA GESTIÓN

~~PARTICIPACIÓN, SEA COMO PARTÍCIPE ACTIVA O COMO PARTÍCIPE INACTIVA;~~ 7. TRANSIGIR, DESISTIR Y APELAR DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES; 8. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. 9. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEA CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES; 10. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. 11. NOTIFICARSE VÁLIDAMENTE DE AQUELLOS ACTOS DEL ORDEN ADMINISTRATIVO O JUDICIAL QUE SE FORMULEN CONTRA LA SOCIEDAD, ASÍ CÓMO ABSOLVER INTERROGATORIOS CON CAPACIDAD PARA CONFESAR; 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A. 12. ADMINISTRAR LOS BIENES MUEBLES O INMUEBLES DE PROPIEDAD DE LA SOCIEDAD LABORATORIOS SÍNTESIS LTDA. & CIA S.C.A., RECAUDAR O RECIBIR POR SUS FRUTOS Y CELEBRAR TODA CLASE DE CONTRATOS RELACIONADOS CON LA ADMINISTRACIÓN. 13. ENAJENAR, ADQUIRIR, PERMUTAR, GRAVAR, ARRENDAR BIENES MUEBLES, PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTIIESIS LTDA & CIA S.C.A, SIN LÍMITE DE CUANTIA. 14. ENAJENAR, PERMUTAR, ADQUIRIR, GRAVAR, ARRENDAR BIENES MUEBLES E INMUEBLES PRESENTES O FUTUROS DE LA SOCIEDAD LABORATORIOS SYNTHESIS LTDA & CIA S.C.A., CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MAS ALTO EN LA FECHA DE CELEBRACIÓN Y TENGA RELACIÓN DIRECTA CON EL DESARROLLO SOCIAL, ASÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DE LA SOCIEDAD GESTORA. 15. TOMAR DINERO EN MUTUO, CON FACULTAD PARA ESTIPULAR TODO TIPO DE INTERESES, PLAZOS Y DEMÁS CONDICIONES Y CELEBRAR CONTRATOS DE CUENTA CORRIENTE; 16. GIRAR, ORDENAR GIRAR, ENDOSAR, PROTESTAR, OTORGAR, ACEPTAR ORDENAR AVALÚOS Y HACER TODA CLASE DE NEGOCIOS RELACIONADOS CON TÍTULOS VALORES CUANDO LA CUANTÍA DE CADA OPERACIÓN INDIVIDUALMENTE CONSIDERADA NO EXCEDA DE SEISCIENTAS VECES EL SALARIO MÍNIMO LEGAL MENSUAL MÁS ALTO EN LA FECHA DE SU CELEBRACIÓN, SÍ COMO LAS QUE EXCEDAN DE ESTA SUMA CON LA EXPRESA AUTORIZACIÓN DEL REPRESENTANTE LEGAL DE LA SOCIEDAD GESTORA. 17. PRESENTAR DECLARACIÓN DE RENTA, PATRIMONIO, IMPUESTOS A LAS VENTAS EN ADMINISTRACIÓN DE IMPUESTOS NACIONES Y MUNICIPALES E INTERPONER LOS RECURSOS Y DECLARACIONES PERTINENTES CONTRA ACTOS DE DICHA ADMINISTRACIÓN CON FACULTAD PARA DEFENDER LOS INTERESES DE LA SOCIEDAD EN ÉSTA MATERIA. 18. DESIGNAR APODERADO ESPECIAL PARA CADA PROCESO JUDICIAL O ADMINISTRATIVO. 19. PRÉSENTAR RECURSOS POR VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR 20. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES 21. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES 22. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE



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CAMARA DE COMERCIO DE BOGOTA

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BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.308 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFienda LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F. SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G. OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS, RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR, RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR. I. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES.

MAIO
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DE LA GESTIÓN

~~N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA.~~

CERTIFICA:

**** REVISOR FISCAL ****

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 28 DE JUNIO DE 2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397034 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	
AGUILLON ROJAS SANDRA MILENA	C.C. 000000047436442
REVISOR FISCAL SUPLENTE	
PRADA SANCHEZ NUBIA MARCELA	C.C. 000001032358923

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE 2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PERSONA JURIDICA	
DELOITTE & TOUCHE LTDA	N.I.T. 000008600058134

CERTIFICA:

PERMISO DE FUNCIONAMIENTO:QUE POR RESOLUCION NO.05952 DEL 11 DE JUNIO DE 1.985, INSCRITA EN ESTA CAMARA DE COMERCIO EL 8 DE JULIO DE 1.985 BAJO EL NO. 172.879 DEL LIBRO IX, LA SUPERINTENDENCIA - DE SOCIEDADES CONCEDIO PERMISO DEFINITIVO DE FUNCIONAMIENTO A LA SOCIEDAD.

CERTIFICA:

QUE POR RESOLUCION NO.09006 DEL 19 DE DICIEMBRE DE 1.986 SUPERINTENDENCIA DE SOCIEDADES INSCRITA EL 16 DE ENERO DE 1.987 BAJO EL NO.204.133 DEL LIBRO IX, SE AUTORIZO A LA SOCIEDAD PARA COLOCAR SETENTA Y CUATRO MIL (\$74.000) ACCIONES DE LAS QUE TIENE EN RESERVA, A SU VALOR NOMINAL DE CIEN PESOS (\$100.00) M/CTE., CADA UNA.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 9 DE MARZO DE 2011, INSCRITO EL 18 DE MARZO DE 2011 BAJO EL NUMERO 01462396 DEL LIBRO IX, COMUNICO LA SOCIEDAD MATRIZ:
- EUROPEAN CHEMICALS & CO
DOMICILIO: (FUERA DEL PAIS)
QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL CON LA SOCIEDAD DE LA REFERENCIA.

CERTIFICA:

***** ACLARACIÓN SITUACIÓN DE CONTROL Y DE GRUPO EMPRESARIAL *****
SE ACLARA LA SITUACIÓN DE CONTROL Y GRUPO EMPRESARIAL INSCRITA CON EL NO. 01462396 DEL 9 DE MARZO DE 2011 DEL LIBRO IX EN EL SENTIDO DE INDICAR QUE SE CONFIGURÓ DESDE EL 19 DE NOVIEMBRE DE 2010.

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE : CARDIOPHARM

MATRICULA NO : 00537358 DE 3 DE MARZO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

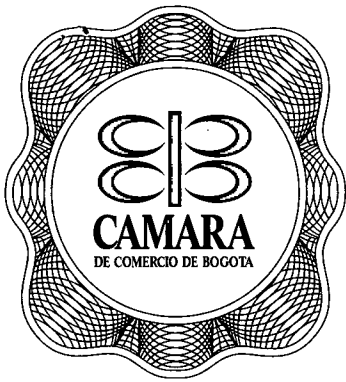
ULTIMO AÑO RENOVADO : 2011

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011



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NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABLES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

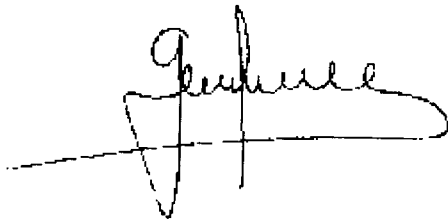
SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 5251 DE 2009.

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A LA CALIDAD
DE LA GESTION

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,
VALOR : \$ 3,700

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

A handwritten signature in dark ink, appearing to be 'Garcia', written over a horizontal line.

ANEXO



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

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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.

(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.

that may irritate the gastric mucosa, such as for instance non-steroidal anti-inflammatory drugs (NSAID), such as diclofenac; antibiotics, such as doxycycline or erythromycin and derivatives thereof; and also substances that need an administration with delayed release.

[0046] The active substance can be provided in the form of a core material that can be prepared from powder or of micro-crystals of the active substance, which may be employed in the form of granules prepared by dry or wet granulation or in the form of pellets or of spheroids prepared by attaching to inert supports and/or extrusion-spheronization.

[0047] I) In a first embodiment, the core material comprising the active substance is prepared by granulation according to the following stages:

[0048] dry mixing the active substance, in the form of a powder or of micro-crystals, optionally with a diluent and an antistatic agent,

[0049] granulating the mixture obtained by spraying with a solution of the binding agent,

[0050] drying.

[0051] For the granulation conventional equipment such as a high-energy granulator, a planetary mixer or a fluidized air bed is used.

[0052] II) In a second embodiment, the core material comprising the active substance is prepared by attaching the active substance to an inert support such as for instance a sugar sphere according to the following stages:

[0053] spraying over inert supports a solution or a suspension comprising the active substance, a dissolved binder and, optionally, a lubricant and an antistatic agent,

[0054] drying.

[0055] The composition to be used for the spraying can be provided, according to the circumstances, in the form of a suspension, in the form of a solution, or in the form of an emulsion in an aqueous or organic media or in the molten state.

[0056] In a first alternative form of the attaching process, the active substance is incorporated in the attaching composition, which is applied to the inert supports.

[0057] According to another alternative form of the attaching process, the active substance is applied by dusting to the inert supports, which are wetted beforehand with the attaching composition.

[0058] All process steps of the present invention can be carried out in conventional equipment such as in a coating pan or a perforated pan or in a fluidized air bed.

[0059] II) According to a third embodiment, the particles comprising the active substance are prepared by extrusion-spheronization.

[0060] The mixture comprising the active substance and the pharmaceutically acceptable excipients is moistened or heated in order to provide satisfactory extrusion, and the extrudates thus obtained are graded and spheronized.

[0061] In the present description, the term "core material" or "active particle" is used to denote without distinction one or other forms under which the active substance can be prepared as pellets, granules or micro tablets, which then are coated with an enteric coating polymer.

[0062] The inert support can be composed of any chemically and pharmaceutically inert excipient existing in the crystalline or amorphous particulate form, for example sugar derivatives, such as lactose, sucrose, hydrolysed starch (malto-dextrin) or celluloses. Mixtures, such as sucrose and starch or mixtures based on cellulose, are also used for the preparation of inert spherical supports. The unit particulate dimension of the inert support can be between 50 μm and 1000 μm , preferably between 200 μm and 710 μm .

[0063] The core material or active particle can additionally comprise one or more excipients chosen from the group consisting of binders, diluents, antistatic agents, and agents for modifying the surrounding micro-pH as well as any mixtures thereof.

[0064] The binder is present in proportions, which can range up to 15% by weight, and according to another aspect up to 10% by weight, with respect to the weight of the uncoated particles. The binder can be chosen from the group consisting in particular of cellulose polymers, acrylic polymers, povidones, copovidones, poly(vinyl alcohol)s, alginic acid, sodium alginate, starch, pregelatinized starch, sugars and their derivatives, guar gum, poly(ethylene glycol)s and any mixtures thereof. One role of the binder is to fasten the active substance to the inert supports without loss of material, or to "stick" together the active substance powder or micro-crystals, and the other excipients, in order to give homogeneous core material with an even distribution of the active substance.

[0065] The diluent is present in proportions, which can range up to 95% by weight, and according to another aspect up to 50% by weight, with respect to the weight of the core material and can be chosen from the group consisting in particular of cellulose derivatives and preferably microcrystalline cellulose, polyols and preferably mannitol, single starches, sugar derivatives, such as lactose, and any mixtures thereof. One role of the diluent is to increase the total mass of core material, which is to be coated and to produce a population of particles of homogeneous size.

[0066] The antistatic agent is present in proportions which can range up to 10% by weight, and according to another aspect up to 3% by weight, with respect to the weight of the uncoated particles and can be chosen from the group consisting in particular of colloidal silica, in particular that sold under the trade name Aerosil®, and according to another aspect precipitated silica, in particular that sold under the name Syloid® FP244, micronized talc, non-micronized talc and any mixtures thereof.

[0067] The antistatic agent improves the fluidization of the material when using a fluidized air bed, and in particular in the case of a powder granulation.

[0068] The agent for modifying the surrounding micro-pH can be an acidic or basic compound. When the pharmaceutically active substance is an acid labile substance, for example proton pump inhibitor, the agent modifying the micro-pH is always a basic compound.

[0031] In the case of the multiparticulate tablet of the invention, the latter disintegrates in the medium with a pH of 1.2, releasing the coated active particles, which are then directly in contact with the medium with a pH of 1.2; the amount of the active substance remaining in the enteric coated particles on conclusion of this test being greater than 95%, preferably greater than 97% and more preferably still greater than 99%.

"Release Test":

[0032] It consists of the determination of the dissolution profile of the enteric coated particles by a dissolution profile derived from that described, for example, in the United States Pharmacopoeia (US Pharmacopoeia, XXth Ed.).

[0033] In a first step, the enteric pharmaceutical dosage form is placed for 120 minutes in a dissolution medium with a pH of 1.2. Then, in a second step, this same enteric coated dosage form is placed for 30 minutes in a medium with a pH, which is increased up to a value of 6.8 by addition of an alkaline buffer solution to the medium from the first step.

[0034] The amount of the active substance released into the medium with at pH 6.8 after 30 minutes is subsequently measured, which makes it possible to directly assess the integrity of the enteric coated particle itself and to confirm that the active substance is indeed immediately released in the second medium.

[0035] The result is expressed as percentage by weight with respect to the total starting amount of the active substance.

[0036] In the present invention, the multiparticulate tablet disintegrates in the medium with a pH of 1.2, releasing the enteric coated particles, which are then directly in contact with the medium with a pH of 1.2 (in which the enteric polymer is insoluble). Then the enteric coated particles are in contact with the medium with a pH of 6.8, at which pH the enteric polymer is soluble and at which pH the active substance, thus will be released. With the tablet of the invention, an amount of greater than 90%, preferably of greater than 95%, is thus released after 30 minutes in a dissolution medium with a pH of 6.8.

[0037] The invention thus relates to a multiparticulate tablet with improved gastro-protection, comprising at least one pharmaceutically active substance in the form of enteric coated particles, and a mixture of tableting excipients. The said mixture of excipients comprising xylitol 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), preferably less than or equal to 31/97 (weight/weight), more preferably still approximately 1/99 (weight/weight).

[0038] According to one aspect the pharmaceutically active substance is a proton pump inhibitor compound. Thus, according to this aspect the invention relates to a multiparticulate tablet with 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 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), preferably less than or equal to 3/97 (weight/weight), more preferably still approximately 1/99 (weight/weight).

[0039] In the present invention, powder "in a directly compressible form" is understood to mean a powder for which the mean diameter of the particles is between 100 μm and 500 μm .

[0040] Pharmaceutically active substances suitable according to the present invention are: Types of pharmaceutically active substances might benefit from a gastro-protection and may be chosen from any family of drugs, for example from gastro-intestinal sedatives, antacids, analgesics, anti-inflammatories, coronary vasodilators, peripheral and cerebral vasodilators, anti-infective, antibiotics, antiviral agents, antiparasitic agents, anticancer agents, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, antihistamines, antidiarrheal agents, laxatives, dietary supplements, immunodepressants, hypocholesterolaemics, hormones, enzymes, antispasmodics, anti-anginal agents, medicinal products that affect the heart rate, medicinal products used in the treatment of arterial hypertension, antimigraine agents, medicinal products that affect blood clotting, antiepileptics, muscle relaxants, medicinal products used in the treatment of diabetes, medicinal products used in the treatment of thyroid dysfunctions, diuretics, anorexiogenic agents, anti-asthmatics, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, antinausea agents, hematopoietic agents, uricosuric agents, plant extracts, contrast agents or any other family of compounds.

[0041] The active substance is provided as such or in the form of a pharmaceutically acceptable salt thereof, and if appropriate in its racemic form or in the form of one of its pure enantiomer or any polymorphic form. With the expression "a pharmaceutically acceptable salt thereof" is meant any basic or acidic salts, such as salts with inorganic or organic acid, such as carboxylic acid; or salts with amines; or salts with alkaline compounds, or similar derivatives.

[0042] According to a specific aspect of the present invention pharmaceutically active substances that need gastro-protection for oral administration are suitable, such as acid labile compounds, which inhibit the proton pump. Such substances are for instance omeprazole, lansoprazole, pantoprazole, pariprazole, leminoprazole and rabeprazole. These substances might be provided in their neutral form or in the form of alkali metal salts, in their racemic form or in the form of their pure enantiomers, or in any polymorphic form.

[0043] The proton pump inhibitor compound, omeprazole, and its (S)-enantiomer, esomeprazole, are well recognised and sold under the trade names Losec® and Nexium®, respectively.

[0044] In the present patent application, the terms "proton pump inhibitor", "PPI" and "compound which inhibits the proton pump" will be used interchangeable to denote any compound of this family. These compounds are present in the neutral form, in the form of an alkali metal salt, in the form of a racemate or of an enantiomer, or in any polymorphic form.

[0045] Other types of pharmaceutically active substances suitable according to the present invention are compounds

[0069] The acidic agent can be composed of any inorganic or organic acid, in the form of the free acid, of an acid anhydride or of an acid salt.

[0070] This acid is chosen from the group consisting in particular of tartaric acid, citric acid, maleic acid, fumaric acid, malic acid, adipic acid, succinic acid, lactic acid, glycolic acid, α -hydroxy acids, ascorbic acid and amino acids, and the salts and derivatives of these acids.

[0071] The basic compound is chosen from the group consisting of potassium carbonate, lithium carbonate, sodium carbonate, calcium carbonate, ammonium carbonate, L-lysine carbonate, arginine carbonate, sodium glycine carbonate, sodium carbonates of amino acids, anhydrous sodium perborate, effervescent perborate, sodium perborate monohydrate, sodium percarbonate, sodium dichloroisocyanurate, sodium hypochlorite, calcium hypochlorite and any mixtures thereof. In the context of the present invention, the carbonate is for instance a carbonate, a sesquicarbonate or a hydrogencarbonate.

[0072] The amount of agent for modifying the surrounding micro-pH is between 0 and 20%, preferably between 5% and 15% and more preferably between 5% and 10% by weight, with respect to the weight of the uncoated core material or active particles.

[0073] One or several optional polymeric layers can be applied between the core material itself and the enteric coating polymer, in order to isolate the active core in the case of possible physicochemical incompatibilities between the components of each of the parts or in order to strengthen the gastro-protection or to improve the stability of the formulation.

[0074] Each optional polymeric layer is composed of at least one film-forming polymeric agent chosen from the same polymers as those used as binder. The film-forming polymeric agent is being used either as binding agent or as a separating layer. The relative amount of polymer is, in the first case, less than or equal to 40% by weight, calculated with respect to the dry mass of the optional polymeric layer. In the second case, the relative amount of polymer is greater than 40% by weight, calculated with respect to the dry mass of the said layer.

[0075] The optional polymeric layer can additionally comprise one or more protective agents, for example a weakly hygroscopic agent, such as mannitol, an opacifying agent, such as titanium dioxide, or also acidic or basic substances, preferably chosen from those used to locally create a micro-pH, or also hydrophobic substances, such as, for example, mono- and diacetylated glycerides (Myvacet®), silicone oils (Dimethicone®) or triglycerides (Gelucire®).

[0076] The optional polymeric coating layer can additionally comprise a plasticizer, a lubricant or adjuvants of the type of those used in the enteric coating layer. In this case, the polymer is chosen from the same polymers as those used as binder.

[0077] The amount of polymer applied is between 1% and 10% as increase in weight with respect to the mass of active cores employed, preferably between 2% and 5%.

[0078] The core material or active particle comprising the active substance is subsequently coated with a film which

provides the gastro-protection of the active substance and which film comprises a film-forming enteric polymer and at least one plasticizer.

[0079] The enteric polymer is chosen from the group consisting of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose succinate phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose, shellac and any other enteric polymer, used alone, as a mixture or combined separately. According to one feature of the invention the enteric polymer is the methacrylic acid copolymers sold under the trade name Eudragit® L100 and Eudragit® L30D.

[0080] The enteric coating composition is applied by spraying in order to form a continuous film covering the entire surface of each active particle. The enteric coating layer is applied in an amount sufficient to provide the gastro-protection of the active substance depending on the situation and surface condition of the core material. The enteric coating is present in proportions, which can range up to approximately 50%, and according to another feature up to approximately 20%, calculated as increase in weight with respect to the mass of active particles to be coated.

[0081] The solvent chosen for spraying the enteric polymer can be water, an organic solvent, such as ethanol, isopropanol or acetone, or any mixture of these solvents.

[0082] The enteric coating polymer is prepared in the form of a solution, suspension or colloidal dispersion in any of the solvent or mixture of solvents. According to a preferred embodiment the enteric coating polymer is prepared in the form of a colloidal dispersion in water.

[0083] Optionally, the enteric coating polymer can be mixed with a second polymer or copolymer, which can itself be soluble or insoluble, in particular a neutral copolymer of esters of acrylic acid and of methacrylic acid sold under the trade name Eudragit® NE30D.

[0084] The addition of a second polymer to the enteric coating composition makes it possible to improve the mechanical properties of the enteric film resulting from this mixture. In this case, the second polymer is added in an amount of at most 100%, calculated as dry weight of polymer with respect to the dry weight of the enteric polymer, and according to a preferred embodiment in a ratio of between 10% and 30%.

[0085] The enteric coating composition can also comprise a plasticizer. The plasticizer is chosen from the group consisting of triethyl citrate, acetyl tributyl citrate, triacetin, tributyl citrate, diethyl phthalate, polyethylene glycols, polysorbates, mono- and diacetylated glycerides, and any mixtures thereof. One role of the plasticizer is to lower the glass transition temperature of the film.

[0086] The plasticizer is usually used in a total proportion of at most 40%, preferably between 10% and 30%, expressed by weight with respect to the dry weight of polymer.

[0087] The enteric coating composition may also optionally comprise a surface-active agent, an antistatic agent or a lubricant. The surface-active agent is chosen from anionic, cationic, nonionic or amphoteric surfactants.

[0088] An antistatic agent is used, for example, to prevent problems related to static electricity. It is chosen from the

group consisting of micronized talc, non-micronized talc, colloidal silica (Aerosil® 200), treated silica (Aerosil® R972), precipitated silica (Syloid® FP244) and any mixtures thereof. The antistatic agent is usually used in a proportion of at most approximately 10% by weight, preferably between 0 and 3%, preferably of less than approximately 1% by weight.

[0089] The lubricant is chosen from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, micronized polyethylene glycols, sodium benzoate and any mixtures thereof.

[0090] The particle size of the coated particles must allow them to be used in the manufacture of multiparticulate tablets. The size is determined by conventional methods, for example using a set of sieves of calibrated mesh size or by laser diffraction. The particle size diameter is between 0.1 and 2 mm, preferably between 0.3 and 1 mm, and more preferably between 0.5 and 1 mm.

[0091] In a preferred embodiment of the process for the preparation of the coated particles, all steps for the preparation of the active particles, and coating steps are carried out in a fluidized air bed. The fluidized air bed is equipped with a spray nozzle, in which the position and the direction of spraying can be chosen. The method of spraying is described as top spray, bottom spray or tangential spray, according to the usual terminology of a person skilled in the art.

[0092] The choice of the method of spraying makes it possible to control the kinetics of growth of the particles and to prevent phenomena of sticking, related to the nature of the active substance, to the binding or coating composition sprayed and to the various processing parameters (temperature, air pressure, for example, flow rate of solution).

[0093] In addition to the particles coated with an enteric polymer, the tablet of the invention comprises a mixture of excipients chosen from the group consisting of at least one diluent, at least one disintegrating agent, at least one lubricant and optionally a swelling agent, an antistatic agent, a binder, an adjuvant and their mixtures, the said mixture of excipients additionally comprising xylitol and/or maltitol, each in a directly compressible form, in a proportion with respect to the amount of the other diluent or diluents of less than 5/95 (weight/weight).

[0094] The multiparticulate tablet is preferably an orodispersible tablet comprising a mixture of tableting excipients chosen from the group consisting of at least xylitol and/or maltitol, each in a directly compressible form, at least one disintegrating agent, at least one 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, tableting excipients chosen from the group comprising swelling agents, antistatic agents, permeabilising agents, sweeteners, flavoring agents and colors.

[0095] Advantageously, the ratio of the amount of xylitol and/or the amount of maltitol to the amount of the other diluent or diluents is less than or equal to 3/97, preferably of approximately 1/99.

[0096] The xylitol and/or the maltitol are each provided in a directly compressible form, that is to say in the form of a

powder for which the mean diameter of the particles is between 100 μm and 500 μm .

[0097] The diluent can be chosen from sucrose, lactose, fructose, dextrose, mannitol, sorbitol, lactitol, erythritol, dicalcium phosphate, tricalcium phosphate or microcrystalline cellulose, alone or as a mixture, in a directly compressible form or in the form of a powder for which the mean diameter of the particles is less than 100 μm .

[0098] Advantageously, the diluent is mannitol.

[0099] The diluent is used in a proportion of between 20% and 90% by weight, preferably between 25% and 60% by weight, calculated with respect to the weight of the tablet.

[0100] The disintegrating agent is chosen from the group consisting in particular of crosslinked sodium carboxymethylcellulose, denoted by the term croscarmellose, crosslinked polyvinylpyrrolidones, denoted by the term crospovidone, and their mixtures.

[0101] The disintegrating agent is used in a proportion of between 1% and 20% by weight, preferably between 5% and 15% by weight, calculated with respect to the weight of the tablet.

[0102] The swelling agent is chosen from the group consisting of microcrystalline cellulose, starches, modified starches, such as sodium starch glycolate or carboxymethylstarch, alginic acid, sodium alginate and their mixtures.

[0103] The swelling agent is used in a proportion, which can range up to 20%, preferably of between 1% and 15%, by weight, calculated with respect to the weight of the tablet.

[0104] The lubricant is chosen from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, polyethylene glycols, sodium benzoate, pharmaceutically acceptable oil, preferably dimethicone or liquid paraffin, and their mixtures.

[0105] The lubricant is always present, either at the heart of the tablet and/or on its surface; it is used in a proportion which can range up to 2%, preferably between 0.02% and 2%, by weight, more preferably between 0.5% and 1% by weight, calculated with respect to the weight of the tablet.

[0106] The antistatic agent can be chosen from the group consisting of micronized talc, nonmicronized talc, colloidal silica (Aerosil® 200), treated silica (Aerosil® R972), precipitated silica (Syloid®) FP244) and their mixtures.

[0107] The antistatic agent is used in a proportion, which can range up to 5% by weight, calculated with respect to the weight of the tablet.

[0108] The binder is used in the dry form and can be a starch, a sugar, polyvinylpyrrolidone or carboxymethylcellulose, alone or as a mixture.

[0109] The binder is used in a proportion, which can range up to 15% by weight, preferably of less than 10% by weight, calculated with respect to the weight of the tablet.

[0110] Adjuvants can also be added to the mixture intended to be tableted and are chosen from the group consisting of pH-adjusting agents, systems which make it possible to produce effervescence, in particular carbon diox-

die generators of the type of those used as pH-adjusting agents, surfactants, sweeteners, flavourings, colorants and mixtures.

[0111] The preparation of the multiparticulate tablet comprising the enteric particles can comprise the following stages:

[0112] dry mixing the coated active particles with the tableting excipients,

[0113] tableting the mixture in order to obtain a unit form.

[0114] In an advantageous method for the preparation of the tablet, the mixing stage itself comprises two stages, the first stage, consisting in mixing the coated active particles with all the tableting excipients except the internal lubricant, and then a second stage, in which the lubricant is added to the first mixture, in all or in part.

[0115] In the latter case, the remaining fraction of the lubricant is sprayed over the walls of the die and punches during tableting, the lubricant then being in the form of a powder, for example magnesium stearate, or of a liquid, for example liquid paraffin.

[0116] The amounts of lubricant used in the internal and/or external phase are adjusted with care so as to prevent an excess from detrimentally affecting the cohesion of the powder bed during the tableting, leading to capping effector breakage within the tablet.

[0117] In another advantageous embodiment, all the lubricant is sprayed over the punches and/or over the internal face of the tableting dies; the second stage of the mixing is then, of course, suppressed.

[0118] The tableting of the mixture can be carried out on an alternating or rotary tableting machine.

[0119] The stresses during the tableting stage can vary from 5 kN to 50 kN and preferably between 5 kN and 15 kN.

[0120] The hardness of these tablets is preferably between 1 and 10 kp, more preferably between 1 and 5 kp, measured according to the method of the European Pharmacopoeia (2.9.8), 1 kp being equal to 9.8 N.

[0121] Preferably, the hardness of the multiparticulate tablet is adjusted so as to obtain friability, measured according to the method of the European Pharmacopoeia, of less than 2%.

[0122] The tablet can be round, oval or oblong in shape, can exhibit a flat, concave or convex surface and can optionally exhibit engravings or be bevelled.

[0123] The tablet generally has a mass of between 0.1 gram and 2.0 grams and a size in diameter of between 6 mm and 18 mm.

[0124] A process for preparing the tablets according to the present invention comprises the following steps:

[0125] preparing of the active particles, i.e. particles comprising the active substance,

[0126] apply an enteric coating on the active particles, optionally after applying a separating layer on the active particles,

[0127] mixing the enteric coated particles with a mixture of tablet excipients comprising xylitol or maltitol, each in a direct compressible form, a disintegrating agent, a lubricant and at least one other diluent, optionally together with at least one additional excipient selected from a swelling agent, an antistatic agent, a binder, an adjuvant and mixtures thereof

[0128] optionally introduce the lubricant in the tablet machine, and

[0129] compress the mixture of enteric coated particle and mixture of tablet excipients to a tablet.

[0130] The examples below illustrate the invention.

Excipients Used

[0131] Directly compressible mannitol: Parreck M300®, sold by Merck.

[0132] Directly compressible xylitol: Xylisorb 300®, sold by Roquette.

[0133] Directly compressible maltitol: Maltisorb P200®, sold by Roquette.

[0134] Directly compressible sorbitol: Neosorb P60W®, sold by Roquette.

[0135] Crospovidone: Kollidon® CL, sold by BASF.

[0136] Aspartame: sold by Nutrasweet.

[0137] Potassium acesulfame: sold by Sunnett.

[0138] Orange and peppermint flavouring: sold by Firmenich.

[0139] Magnesium stearate: sold by Peter Graven.

[0140] Citric acid: sold by Jungbunzlauer.

Equipment

[0141] The mixer is an inversion mixer with multiple axes of rotation with a capacity of 0.5 to 2 l supplied by Turbula.

[0142] The tableting machine is a SVIAC rotary press equipped with 6 stations of type B for tableting.

Methods

[0143] Hardness: Schleuniger durometer device, method EP, 4th Ed., 2.9.8,

[0144] Test of integrity of the film: Type II paddle device, USP, 100 revolutions/minute, 500 ml 0.1N HCl medium (pH 1.2),

[0145] Release test: type II paddle device, USP, 100 revolutions/minute, 300 ml 0.1N HCl medium (pH 1.2), then 1000 ml pH 6.8 buffer (by addition to the medium of 700 ml of $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$),

[0146] HPLC (S)-omeprazole assay: UV detection at 302 nm.

EXAMPLE 1

[0147] The microgranules, coated with an enteric polymer, comprise magnesium salt of the (S)-omeprazole (esomeprazole Mg) as active substance.

[0148] These microgranules are manufactured according to the teaching of the prior art (WO 96/01623) to produce a

stable formulation. The content of WO 96/01623 is hereby incorporated by reference. The coated micro-granules are prepared according to Example 2 of WO 96/01623, by re-placing omeprazole Mg with (S)-omeprazole Mg.

1) Mixtures

[0149] The mixture of powders is prepared according to the formulation in Table 1.

TABLE 1

Formulations (% w/w)	A	B	C
Coated pellets*	32.2	32.2	32.2
Mannitol	53.8	53.2	51.1
Xylitol	—	0.6	2.7
Crospovidone	10.0	10.0	10.0
Aspartame	0.5	0.5	0.5
K acesulfame	1.0	1.0	1.0
Peppermint flavouring	1.5	1.5	1.5
Magnesium stearate	1.0	1.0	1.0

*Coated pellets of (S)-omeprazole Mg

[0150] Three types of mixtures were prepared, each differing in their respective composition of diluent: the first batch (A) does not comprise xylitol, the batch (B) comprises directly compressible xylitol in a ratio by weight of 1/99 with respect to the mannitol 300M, and batch (C) comprises directly compressible xylitol in a ratio by weight of 5/95 with respect to the mannitol.

[0151] A first mixture, comprising all the constituents of the formulation except magnesium stearate and in the proportions given in Table 1, is prepared over 5 min at 30 revolutions per minute.

[0152] The lubricant is added to the mixture thus obtained by mixing (lubricating stage) for 1 minute at the rate of 30 revolutions/minute.

2) Tableting

[0153] The mixture obtained in the preceding stage is introduced into the feed hopper of the tableting machine; itself equipped with round, flat and bevelled punches with a diameter of 12 mm.

[0154] The tablets prepared have a theoretical mass of 650 mg and comprise a dose of 40 mg calculated as csomeprazole.

[0155] These tablets have the following physical and chemical characteristics (Table 2):

TABLE 2

	A	B	C
Weight (mg) (n = 10)	651.7	652.7	645.7
Hardness (N) (n = 10)	45	45	42
Test of integrity of the film (% w/w)	92.2	99.6	91.9
Release test (% w/w)	84.4	91.4	85.6

3) Conclusions

[0156] The formulation (B), comprising the xylitol in a ratio by weight of 1/99 with respect to the mannitol, exhibits a better suitability for tableting than the formulations (A) and (C); the test of integrity of the film makes it possible to

confirm the absence of detrimental change in the enteric coating film, the amount of (S)-omeprazole released and decomposed in a medium with a pH of 1.2 being less than 1% w/w.

[0157] The gastro-resistance properties of the multiparticulate tablet are therefore improved.

[0158] On the other hand, this effect is not observed for the formulation (C) comprising a xylitol/mannitol ratio of 5/95.

EXAMPLE 2

[0159] Four tablet formulations were prepared as in Example 1 above using the components given in Table 3 below.

TABLE 3

Formulations (% w/w)	D	E	F	G
Coated (S)-omeprazole Mg	31.5	31.5	31.5	31.5
Mannitol	53.5	53.5	53.5	53.5
Xylitol	—	0.5	—	—
Sorbitol	—	—	0.5	—
Maltitol	—	—	—	0.5
Crospovidone	10.0	10.0	10.0	10.0
Aspartame	0.5	0.5	0.5	0.5
K acesulfame	1.0	1.0	1.0	1.0
Flavouring	1.6	1.6	1.6	1.6
Citric acid	0.4	0.4	0.4	0.4
Precipitated silica	0.5	—	—	—
Magnesium stearate	1.0	1.0	1.0	1.0

[0160] The physicochemical properties of the tablets thus obtained were measured as in Example 1 and the results are given in Table 4.

TABLE 4

	D	E	F	G
Weight (mg) (n = 10)	651.4	650.5	647.5	647.6
Hardness (N) (n = 10)	47	46	48	46
Test of integrity of the film (% w/w)	92.5	100.0	88.8	99.0
Release test (% w/w)	—	99.9	89.8	88.6

3) Conclusions

[0161] The formulations (E) and (G), respectively comprising the xylitol and the maltitol in a ratio by weight of 1/99 with respect to the mannitol, exhibit a better suitability for tableting than the formulations (D) and (F); the test of integrity of the film makes it possible to confirm the absence of detrimental change in the enteric coating film, the amount of (S)-omeprazole released and decomposed in a medium with a pH of 1.2 being less than 1% w/w.

[0162] Their gastro-resistance properties are therefore improved.

[0163] On the other hand, this effect is not observed for the formulation (F), comprising sorbitol in a sorbitol/mannitol ratio of 1/99.

1. A multiparticulate tablet comprising a pharmaceutically active substance in the form of enteric-coated particles, and a mixture of tableting excipients, wherein the mixture of excipients comprises: a first diluent selected from the group consisting of xylitol, maltitol, and mixtures thereof, wherein

the first diluent is in a directly compressible form; a disintegrating agent; a lubricant; and at least one other diluent, and wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 5/95 (weight/weight); and wherein the result of the "test of integrity of the film" is greater than 95%, and the result of the "release test" is greater than 90%.

2. The multiparticulate tablet according to claim 1, wherein the pharmaceutically active substances is chosen from the group consisting of gastrointestinal sedatives, antacids, analgesics, anti-inflammatories, coronary vasodilators, peripheral and cerebral vasodilators, anti-infectives, antibiotics, antiviral agents, antiparasitic agents, anticancer agents, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, antihistamines, antidiarrheal agents, laxatives, dietary supplements, immunodepressants, hypocholesterolaemics, hormones, enzymes, antispasmodics, anti-anginal agents, medicinal products that affect the heart rate, medicinal products used in the treatment of arterial hypertension, antimigraine agents, medicinal products that affect blood clotting, anti-epileptics, muscle relaxants, medicinal products used in the treatment of diabetes, medicinal products used in the treatment of thyroid dysfunctions, diuretics, anorexigenic agents, anti-asthmatics, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, anti-nausea agents, hematopoietic agents, uricosuric agents, plant extracts, and contrast agents.

3. A multiparticulate tablet comprising a proton pump inhibitor in the form of enteric-coated particles, and a mixture of tableting excipients, wherein the mixture of excipients comprises: a first diluent selected from the group consisting of xylitol, maltitol, and mixtures thereof, wherein the first diluent is in a directly compressible form; a disintegrating agent; a lubricant; and at least one other diluent, and wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 5/95 (weight/weight); and wherein the result of the "test of integrity of the film" is greater than 95%, and the result of the "release test" is greater than 90%.

4. A multiparticulate tablet comprising a pharmaceutically active substance in the form of enteric-coated particles, and a mixture of tableting excipients, wherein the mixture of excipients comprises: a first diluent selected from the group consisting of xylitol, maltitol, and mixtures thereof, wherein the first diluent is in a directly compressible form; a disintegrating agent; a lubricant; and at least one other diluent; and wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 5/95 (weight/weight).

5. The multiparticulate tablet according to any one of claims 1 and 4, wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 3/97 (weight/weight).

6. The multiparticulate tablet according to claim 5, wherein the ratio of a) the first diluent to b) the other diluent(s) is approximately 1/99 (weight/weight).

7. A multiparticulate tablet comprising a proton pump inhibitor in the form of enteric-coated particles, and a mixture of tableting excipients, wherein the mixture of excipients comprises: a first diluent selected from the group consisting of xylitol, maltitol, and mixtures thereof, wherein the first diluent is in a directly compressible form; a disintegrating agent; a lubricant; and at least one other diluent; and wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 5/95 (weight/weight).

8. The multiparticulate tablet according to any one of claims 3 and 7, wherein the ratio of a) the first diluent to b) the other diluent(s) is less than 3/97 (weight/weight).

9. The multiparticulate tablet according to claim 8, wherein the ratio of a) the first diluent to b) the other diluent(s) is approximately 1/99 (weight/weight).

10. The multiparticulate tablet according to any one of claims 3 and 7, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, an alkaline salt of omeprazole, esomeprazole, and an alkaline salt of esomeprazole.

11. The multiparticulate tablet according to any one of claims 1, 3, 4, or 7, wherein the mixture of tablet excipients optionally further comprises one or more additional agents selected from the group consisting of swelling agents, anti-static agents, binders, adjuvants, and mixtures thereof.

12. The multiparticulate tablet according to claim 11, wherein the enteric coating comprises one or more substances selected from the group consisting of cellulose acetate phthalate, hydroxypropylmethyl-cellulose phthalate, hydroxypropylmethylcellulose succinate phthalate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose, shellac, an enteric polymer, and mixtures thereof.

13. The multiparticulate tablet according to claim 11, wherein the enteric coating is applied in an amount of up to about 50%, calculated as an increase in weight with respect to the mass of active particles to be coated.

14. (canceled)

15. The multiparticulate tablet according to claim 11, which is an orodispersible tablet.

16. (canceled)

17. (canceled)

18. The multiparticulate tablet according to claim 15, wherein the disintegrating agent is present in an amount of 1% to 20% by weight, calculated with respect to the total tablet weight.

19. The multiparticulate tablet according to claim 15, wherein the other diluent is present in an amount of 20% to 90% by weight, calculated with respect to the total tablet weight.

20. A process for the preparation of a multiparticulate tablet according to any one of claims 1, 3, 4, and 7, wherein the process comprises the following steps:

a) preparing active particles comprising a pharmaceutically active substance;

b) applying an enteric coating on the active particles;

c) mixing the enteric-coated particles with a mixture of tablet excipients comprising: a first diluent selected from the group consisting of xylitol, maltitol, and combinations thereof, wherein the first diluent is in a direct compressible form; a disintegrating agent; a lubricant; and at least one other diluent, optionally together with one or more additional excipients selected from swelling agents, antistatic agents, binders, adjuvants, and mixtures thereof; and

d) compressing the mixture of enteric-coated particles and tablet excipients to form a tablet.

21. A method for treating gastrointestinal diseases, which comprises administering to a patient in need thereof a multiparticulate tablet according to any one of claims 3 and 7.

22. The multiparticulate tablet according to claim 10, wherein the alkaline salt of omeprazole or esomeprazole is a magnesium salt.

23. The process according to claim 20, further comprising applying an optional separating layer on the active particles prior to applying the enteric coating.

24. The process according to claim 20, wherein the lubricant lubricates an internal or external phase of the tablet.

* * * * *

DIRECCIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. PCT 10-41742

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **626** DE

FECHA **22 DE MARZO DE 2011** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **17 DE JUNIO DE 2011**

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 X

NO

2020
Bogotá, D.C.,

Doctora:
Margarita Castellanos Abondano.
Apoderada

Oficio N°: 010889

ASUNTO:

Radicación PCT N°	10-041742
Trámite	011
Evento	378
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Laboratorios SYNTHESIS S.A.S., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

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.



CARLOS DANIEL LEMUS GIRALDO.
Profesional Universitario 2044-09 (P).
Con asignación de funciones de la
Dirección de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 14 JUL. 2011.

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