

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: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 08 079827
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES FARMACÉUTICAS PARA LA
ERRADICACIÓN DE HELICOBACTER PYLORI"
Solicitante : FERRER INTERNATIONAL, S.A.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 612 del 29 de enero de 2010

Yo, *CIELO ANGELA PEÑA RODRIGUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. *82701* del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** 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 "COMPOSICIONES FARMACÉUTICAS PARA LA ERRADICACIÓN DE HELICOBACTER PYLORI", cuyo titular es **FERRER INTERNATIONAL, S.A.**, 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 claritromicina y un compuesto de amoxicilina. 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 31 de julio de 2008 reivindicando prioridad bajo la solicitud EP20060100029 del 2006-01-03; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010, cuya publicación internacional corresponde a la WO2007077158 del 12/07/2007.

2.2. La solicitud colombiana 08 079827 objeto de la presente oposición, se refiere a una composición de granulado para la administración oral que comprende simultáneamente un inhibidor de la bomba de protones, un compuesto de claritromicina y un compuesto de amoxicilina. Composiciones que son

adecuadas para llenarse en sobres y son útiles en el tratamiento de trastornos asociados con la bacteria *Helicobacter*.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra 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"*. Así las cosas, 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: WO2005058282 publicada el 30 de mayo de 2005.

2.4. Ahora bien, el documento D1, particularmente en la página 14, la página 15, y en el ejemplo 1 que comprende una píldora que comprende un núcleo omeprazol, una capa protectora, una capa entérica de polimetacrilato, una capa de recubrimiento que comprende un antibiótico, claritromicina y una capa externa final. Así las cosas, considerando el documento D1, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir del documento D1, el hecho de concebir una composición de granulado para la administración oral que comprende simultáneamente un inhibidor de la bomba de protones, un compuesto de claritromicina y un compuesto de amoxicilina que es útil para el tratamiento de trastornos asociados con la bacteria *Helicobacter*. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.5. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08 079827 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.6.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 03 de enero de 2006, a partir del documento D1, es posible llegar de manera evidente a una composición de granulado para la administración oral que comprende simultáneamente un inhibidor de la bomba de protones, un compuesto de claritromicina y un compuesto de amoxicilina, que es adecuadas para llenarse en sobres y que es útil en el tratamiento de trastornos asociados con la bacteria *Helicobacter*, sobre la cual busca protección en el capítulo reivindicatorio.

2.7. 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 uno de los tres requisitos de patentabilidad.

2.8. 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 **“COMPOSICIONES FARMACÉUTICAS PARA LA ERRADICACIÓN DE HELICOBACTER PYLORI”**, cuyo titular es **FERRER INTERNATIONAL, S.A.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 612 del 29 de enero de 2010.

3. PRUEBAS

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

- D1: WO2005058282 publicada el 30 de mayo de 2005.

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.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-079827 - 00003-0000

Fecha: 2010-04-27 10:59:24 Dep. 2020 DIR.NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 45

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 32,630
FECHA : ABRIL 27 DE 2010

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	174684996	07/04/2010	590,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	174685000	07/04/2010	1,475,000.00

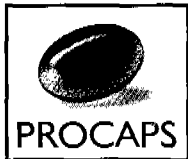
***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 079.827, titulada "COMPOSICIONES FARMACÉUTICAS PARA LA ERRADICACIÓN DE **HELICOBACTER PYLORI**", cuyo titular es **FERRER INTERNATIONAL, S.A.**, publicada en la gaceta No. 612 del 29 de enero de 2010.

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 Barranquilla (Colombia) a los 12 días del mes de abril de 2010.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

CIELO ANGELA PEÑA RODRIGUEZ

C.C. 51'940.252 de Bogotá

T.P.A. 82701 del C.S. de la J.



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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303718-3303716.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----- limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".-----

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS..

PROCAPS S.A.-----

NIT: 890.106.527-5.

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A.

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:

***** C O N T I N U A *****



***** Pag. 2
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

PROCAPS S.A.-----
SIGLA: PROCAPS.
DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas,

***** C O N T I N U A *****

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de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

***** C O N T I N U A *****



***** Pag. 3
C A M A R A D E C O M E R C I O
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07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

CC.*****7,463,982

CC.*****7,461,324

CC.*****8,671,834

Suplentes

1. Minski Zirberblum Elliot

CC.*****72,219,541

***** C O N T I N U A *****

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C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5.

2. Minski Deitel Daniel
3. Minski Sharon

PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa Walter	CC.*****16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Duarte Diaz David	CC.*****73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organó Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por

***** C O N T I N U A *****

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***** Pag. 5
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
07*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin ----- representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ---- confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ----- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ----- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ----- VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ----- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ---- amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA ----- CC.No.8.715.941, para que en nombre y representación de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como tambien los demas documentos relacionados con ellas, ----- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al señor MARLON ---- TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de ---- PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio ---- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ---- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----- representación de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----- (1.000.000.000.00) M.L. CUARTO: EI representante legal de la ---- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ----- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.

NIT: 890.106.527-5.

bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que
comparece en su condicion de Presidente y Representante Legal de la
Sociedad PROCAPS S.A., confiere por medio de este instrumento -----
publico Poder especial Amplio y Suficiente a la doctora MILENA -----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda -----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores
de documentos referentes a reforma, disolución, liquidación o
nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 30 de Marzo de 2010.

La información sobre embargos de establecimiento se suministra en
Certificados de Matrícula, la de contratos sujetos a registro, en
Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco
días hábiles despues de la correspondiente inscripción, siempre
que, dentro de dicho término, no sean objeto de los recursos de
reposición ante esta entidad, y/o de apelación para ante la
Superintendencia de Industria y Comercio.

m. Rojas

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(71) Applicant (for all designated States except US): **KOREA UNITED PHARM, INC** [KR/KR]; 154-8 Nonhyun-dong, Kangnam-ku, Seoul 135-010 (KR).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **AHN, Ki-Young** [KR/KR]; 1610 Uncheon-dong, Heungduk-gu, Cheongju-si, Chungcheongbuk-do 361-110 (KR). **GIL, Young-Sig** [KR/KR]; 810-1506, Buyoung APT 320 Keumcheon-dong Sangdang-gu, Cheongju, Chungcheongbuk-do 360-803 (KR). **YU, Chang-Hun** [KR/KR]; Boyoung APT 401, 153-1 Keumgu-ri Okcheon-eup, Okcheon-gun, Chungcheongbuk-do 373-800 (KR).

KIM, Hye-Kyeong [KR/KR]; 55-15, Jeomchon-dong, Mungyeong-si, Gyeongsangbuk-do 745-886 (KR). **AHN, Geon-Seok** [KR/KR]; 207th Yeong-gwang APT 538-1, Seojong-dong, Pyongtaek-si, Gyeonggi-do 459-812 (KR). **HONG, Seok-Cheon** [KR/KR]; Kangkyung APT ma-140, 109 Hongkyo-ri Kangkyung-cup, Nonsan, Chungcheongnam-do 320-903 (KR). **YANG, Geun-Woo** [KR/KR]; 839 Galma-2dong, Seo-gu, Daejeon 302-809 (KR).

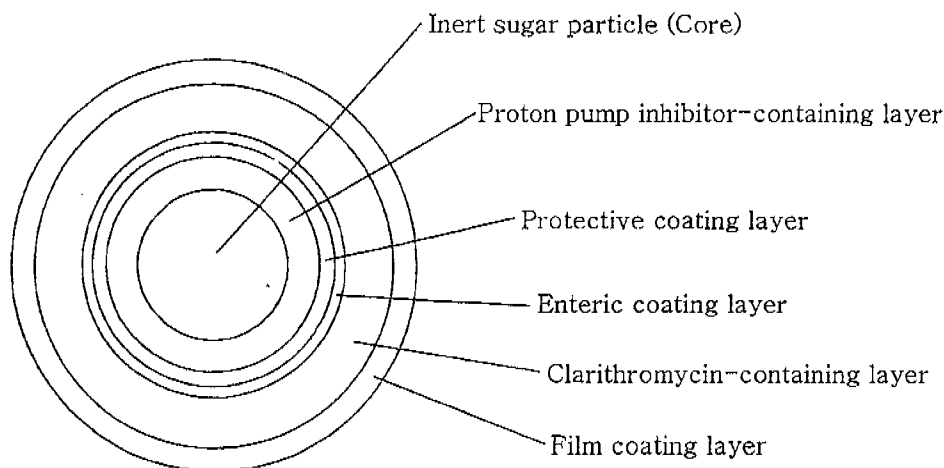
(74) Agent: **KIM, Hong-Gyun**; 4F Wooyoung Building 637-20 Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, GU, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM).

[Continued on next page]

(54) Title: DOUBLE PELLET FORMULATION OF PROTON PUMP INHIBITORS AND CLARITHROMYCIN FOR THE TREATMENT OF GASTROINTESTINAL ULCER, AND METHOD FOR PRODUCING THE SAME



(57) Abstract: The present invention relates to a double pellet formulation effective for the treatment of various peptic ulcers, including a peptic ulcer caused by *Helicobacter pylori*, as well as a preparing method thereof. More particularly, the present invention relates to a double pellet formulation in which layers separated from each other are formed in one pellet, and a proton pump inhibitor and antibiotic clarithromycin are contained in the separated layers, respectively, such that upon administration of the formulation, the drugs can be released in different sites of the living body in a more stable form, thus maximizing a therapeutic effect against various peptic ulcers, including a peptic ulcer caused by *Helicobacter pylori*, as well as a preparing method thereof.

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DOUBLE PELLET FORMULATION OF PROTON PUMP INHIBITORS AND
CLARITHROMYCIN FOR THE TREATMENT OF GASTROINTESTINAL ULCER,
AND
METHOD FOR PRODUCING THE SAME

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Technical Field

The present invention relates to a double pellet formulation effective for the treatment of various peptic
10 ulcers, including a peptic ulcer caused by *Helicobacter pylori*, as well as a preparing method thereof. More particularly, the present invention relates to a double pellet formulation in which layers separated from each other are formed in one pellet, and a proton pump inhibitor
15 and antibiotic clarithromycin are contained in the separated layers, respectively, such that upon administration of the formulation, the drugs can be released in different sites of the living body in a more stable form, thus maximizing a therapeutic effect against
20 various peptic ulcers, including a peptic ulcer caused by *Helicobacter pylori*, as well as a preparing method thereof.

Background Art

25 For the treatment of peptic ulcers, various therapies are used, and of them, a therapy is mainly used wherein at least two active ingredients are administered at the same time or at some intervals. In the most general administration method, the drugs are formulated separately
30 and administered at the same or different time, thus exhibiting their therapeutic effects. This method has a significant problem in that it causes patients to keep the drug administration time.

Of various therapies for the treatment of peptic ulcers, the most generally used therapy may be one associated with a digestive system disease caused by microorganism *Helicobacter pylori*, and digestive system diseases, such as gastritis and stomach-duodenal ulcer, which can develop into the form of tumors. As known already, *Helicobacter pylori*, which is a bacterium which had been called *Campylobacter pylori*, is a classification name changed recently. It is a pathogenic bacterium found in 1983, and is known as a pathogenic factor acting as a background for upper digestive tract diseases, such as peptic ulcers (e.g., stomach ulcer and duodenal ulcer), inflammations (e.g., gastritis) and stomach cancer, mucosa-associated lymphoid tissue (MALT) lymphoma, or chronic heart diseases.

At present, studies on the treatment of *Helicobacter pylori* infection are being actively conducted, and there are many reports of therapeutic methods for removing *Helicobacter pylori* as well as therapeutic methods for preventing the recurrence of *Helicobacter pylori* infection. Such therapeutic methods include either the administration of a single formulation, such as bismuth, an antibiotic, a proton pump inhibitor or an anti-ulcer agent, or the administration of a combination of two or three of such substances. However, in such therapeutic methods still have many problems to be solved, in that administration frequency is high, the administration of a larger amount than usual dose may be required, and symptoms, such as diarrhea or constipation, and resistant bacteria, occur due to drug administration.

US Patent No. 5,196,205 discloses a method for the treatment of the *Helicobacter pylori* infection, the method

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comprising administering a first antibiotic selected from a bismuth compound, penicillin and tetracycline, and a second antibiotic such as metronidazole. Also, this therapeutic method comprises administering three tablets each
5 containing one active ingredient, several times each day. Thus, this therapeutic method has a shortcoming in that it is very complex, thus making patient drug compliance poor.

Furthermore, US Patent No. 5,196,205 discloses a therapeutic method using four active ingredients comprising
10 omeprazole which irreversibly inhibits a proton pump to reduce gastric acid secretion, in addition to the above three active ingredients. Of the four active ingredients, omeprazole must be administered at a time different from the remaining three ingredients, and the administration
15 time can be determined depending on disease severity, patient age, and other factors which may influence the effect of omeprazole.

The combined therapeutic method requiring a complex posology, disclosed in said patents, has a problem in that
20 a case where a therapeutic effect is not achieved is liable to occur.

US Patent Nos. 5,472,695, 5,560,912 and 5,582,837, and WO Nos. 92/11848 and 96/02237 disclose single or combined therapeutic methods for eradicating *Helicobacter*
25 *pylori*. However, the therapeutic methods disclosed in such patents did not achieve a satisfactory effect in preparing active ingredients into one formulation while more fundamentally overcoming the problem of interaction between the active ingredients.

30 Korean patent laid-open publication No. 2001-0033244 discloses a method for preparing a double capsule by filling active ingredients for combined therapy into two

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capsules and filling the smaller capsule of the two capsules into the larger capsule. However, this method has low operation efficiency as well as a very high possibility that the filling operation cannot be smoothly performed due to the already filled capsule or already filled other drugs. Thus, this method may have many problems upon mass production.

Furthermore, US patent Nos. 5,310,555 and 5,501,857 disclose technologies of using the double capsule to administer nutritive components to animals. However, they also have the above-mentioned problems and thus cannot be considered as preferred methods.

Of combined therapies for eradicating *Helicobacter pylori*, active ingredient combinations listed below was clinically tested on the human body, and test methods thereof were already reported. Examples of combinations of more than two drugs are as follows:

- amoxicillin, metronidazole and furazolidone;
- bismuth subsalicylate, lansoprazole and clarithromycin
- bismuth subsalicylate, roxithromycin, metronidazole and ranitidine;
- clarithromycin, colloidal bismuth subcitrate and furazolin;
- colloidal bismuth subcitrate, amoxicillin and metronidazole;
- ebrotidine, amoxicillin and metronidazole;
- lansoprazole, amoxicillin and azithromycin;
- lansoprazole, amoxicillin and clarithromycin;
- lansoprazole, amoxicillin and rebamipide;
- lansoprazole, clarithromycin and furazolin;
- lansoprazole, azithromycin and metronidazole;

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- lansoprazole, miconazole and amoxicillin;
- lansoprazole and norfloxacin;
- metronidazole and dirythromycin;
- omeprazole, amoxicillin and azithromycin;
- 5 -omeprazole, amoxicillin, clarithromycin and
metronidazole;
- omeprazole, amoxicillin, metronidazole and bismuth;
- omeprazole, amoxicillin and rebamipide;
- omeprazole, amoxicillin and tinidazole;
- 10 -omeprazole and amoxicillin;
- omeprazole and azithromycin;
- omeprazole, bismuth and ciprofloxacin;
- omeprazole, bismuth and clarithromycin;
- omeprazole, clarithromycin and tinidazole;
- 15 -omeprazole and dirythromycin;
- omeprazole, lansoprazole and rebamipide;
- omeprazole, metronidazole and amoxicillin;
- omeprazole, metronidazole and azithromycin;
- omeprazole, metronidazole and clarithromycin;
- 20 -omeprazole and norfloxacin;
- omeprazole, sucralfate, metronidazole and
tetracycline;
- omeprazole, clarithromycin and tinidazole;
- pantoprazole, clarithromycin and amoxicillin;
- 25 -pantoprazole and clarithromycin;
- ranitidine bismuth citrate, clarithromycin and
tetracycline;
- ranitidine bismuth citrate and clarithromycin;
- ranitidine bismuth citrate, metronidazole and
30 clarithromycin;
- ranitidine bismuth citrate and cefuroxime;

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- rifaximin and erythromycin;
- omeprazole, bismuth, tetracycline and metronidazole;
- omeprazole, bismuth subcitrate, tetracycline and metronidazole; and
- 5 -bismuth subcitrate, tetracycline and metronidazole.

Disclosure of Invention

The present invention has been made to solve the
10 above-mentioned problems occurring in the prior art, and an
object of the present invention is to provide a double
pellet formulation in which layers separated from each
other are formed in one pellet, and a proton pump inhibitor
and antibiotic clarithromycin are contained in the
15 separated layers, respectively, such that upon
administration of the formulation, the drugs can be
released in different sites of the living body in a more
stable form, thus maximizing various peptic ulcers,
including a peptic ulcer caused by *Helicobacter pylori*, as
20 well as a preparing method thereof.

Brief Description of Drawings

FIG. 1 is a schematic diagram showing a double pellet
25 formulation containing a proton pump inhibitor and
antibiotic clarithromycin, according to an embodiment of
the present invention.

Best Mode for Carrying Out the Invention

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The inventive double pellet formulation with a

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spherical pellet shape is characterized in that it is prepared by the steps of: dissolving a proton pump inhibitor, an alkalinizing agent together with a coating base in a solvent, to prepare a coating solution; coating
5 the coating solution on an inert sugar particle; subjecting the coated particle to protective coating and then to enteric coating, so as to prepare a formulation capable of protecting the proton pump inhibitor, an acid-unstable drug; and coating the outer layer of the formulation with
10 an antibiotic together with a coating base.

The inventive double pellet formulation contains two or three active ingredients. In other words, the inventive formulation contains one proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole,
15 pantoprazole and rabeprazole, and one or two antibiotics selected from the group consisting of erythromycin, clarithromycin, azithromycin, tetracycline, tinidazole and metronidazole selectively.

In the present invention, a formulation may be prepared in the form of a double pellet which can be filled into a hard capsule. Namely, it can be prepared either in the form of a multi-layer composite pellet by forming a layer containing a proton pump inhibitor, such as omeprazole, on an inert core, subjecting the coated core to
20 protective coating and enteric coating, and then forming a layer containing an antibiotic, such as clarithromycin, on the enteric coating layer, or in the form of a composite tablet having different layers. Alternatively, it may also be prepared in the form of a double core tablet, such that
25 one or two drugs are contained in a core tablet, and one or two other drugs are contained in an outer layer. It is preferably prepared in the double pellet or double core
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tablet form, and particularly preferably the double pellet form.

The inventive double pellet formulation is prepared by dissolving a proton pump inhibitor and an alkalizing agent together with a coating base in a solvent, and then
5 coating the solution on an inert sugar particle.

The innermost part of the inventive double pellet formulation preferably contains one proton pump inhibitor selected from the group consisting of omeprazole, lansoprazole, pantoprazole and rabeprazole. At this time,
10 it is very important in view of the stability of the formulation that an alkalizing agent is also contained in the innermost part. The alkalizing agent is preferably selected from the group consisting of meglumine, eglumine,
15 diethanolamine, monoethanolamine, triethanolamine, talc, magnesium hydroxide, magnesium oxide, sodium monohydrogen phosphate, potassium monohydrogen phosphate, arginine, lysine, histidine and a mixture of two thereof.

After the inert sugar particle is coated with the
20 solution of the proton pump inhibitor, the alkalizing agent and the coating base, the coated sugar particle is subjected to protective coating in order to protect the acid-unstable drugs. The protective coating base, which can be used in the protective coating, is selected from the
25 group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone and a mixture of two thereof.

Also, the inventive double pellet formulation may be prepared by coating the coated core material with at least
30 one enteric coating layer as a separate layer using a suitable coating technique. Examples of an enteric coating base which is used in the enteric coating include

methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate butylate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, 5 carboxymethylcellulose, shellac, and other suitable enteric coating bases. One or a mixture of two of such enteric coating bases is used as a solution or dispersion in water or any suitable organic solvent. In view of environmental factors such as environmental pollution prevention, a 10 water-based coating process is preferably performed. In this water-based coating process, a water dispersion containing methacrylic acid copolymer is most preferably used as a solvent.

In order to impart preferred mechanical properties 15 and soft and hard properties to the enteric coating layer, the enteric coating layer may contain a pharmaceutically acceptable plasticizer. Examples of such a plasticizer include triacetin, citric acid, ester, phthalic acid ester, dibutyl sebacate, cetyl alcohol, polyethylene glycol, and 20 polysorbate. The amount of the plasticizer can be suitably selected depending on the kind and amount of the enteric coating layer polymer selected and the kind of the plasticizer selected. Also, an increase in the thickness of the coating layer can make acid-sensitive active 25 ingredients resistant against acidic gastric juice.

In order to protect the acid-sensitive active ingredients from the acidic gastric juice, the thickness of the enteric coating layer is preferably at least about 10 μm .

30 The pellet or tablet core coated with the enteric coating layer may be further coated with at least one upper

coating layer. However, unless a great problem in the stability of the formulation is not caused, the additional coating layer does not need to be formed.

The outer layer of the enteric-coated formulation is coated with an antibiotic together with a coating base, so as to prepare a double pellet formulation with a spherical pellet shape. At this time, the antibiotic may be added as either a solution completely dissolved in a suitable solvent, or a dispersion containing fine particles.

The antibiotic which can be contained in the inventive double pellet formulation is selected from the group consisting of a macrolide antibiotic, an imidazole antibiotic, a tetracycline antibiotic and a mixture of two thereof.

Examples of the macrolide antibiotic include erythromycin, clarithromycin, azithromycin, and roxithromycin.

Examples of the imidazole antibiotic include metronidazole, apronidazole, azomycin, benzonidazole, carnidazole, demetridazole, etanidazole, flunidazole, misonidazole, nimorazole, ornidazole, panidazole, ronidazole, and tinidazole.

Examples of the tetracycline antibiotic include tetracycline, chlorotetracycline, doxycycline, glycocycline, guamecycline, lymecycline, metacycline, and sancycline.

When the double pellet or double tablet prepared by the above method is administered to a patient, the outermost layer of the formulation is first disintegrated to release the antibiotic present therein. The released drug acts on *Helicobacter pylori* of gastrointestinal tract mucosa to kill it, and as the formulation reaches the upper portion of the small intestines some time after its

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administration, the proton pump inhibitor contained in the innermost layer is released to perform anti-ulcer action such as the inhibition of gastric acid secretion.

In other words, the prior formulation for the treatment of peptic ulcers had inconvenience resulting from several administrations, since the proton pump inhibitor and the antibiotics were administered separately. On the other hand, the inventive double pellet formulation can be administered to a patient in a more convenient manner and exhibits an excellent therapeutic effect against peptic ulcers.

In a preferred embodiment of the present invention, the inventive double pellet formulation may comprise 1-4% by weight, based on the total weight of the formulation, of the proton pump inhibitor, 30-70% by weight of the antibiotic, 5-15% by weight of hydroxypropylcellulose or a derivative thereof, 0.1-7% by weight of the alkalizing agent, 0.1-2% by weight of polyethylene glycol, 2-7% by weight of the enteric coating base, and 15-30% by weight of the inert sugar particle.

In another preferred embodiment of the present invention, the inventive double pellet formulation may comprise 1-4% by weight, based on the total weight of the formulation, of the proton pump inhibitor, 30-70% by weight of the antibiotic, 5-15% by weight of hydroxypropylcellulose or a derivative thereof, 0.1-7% by weight of the alkalizing agent, 0.1-2% by weight of polyethylene glycol, 2-7% by weight of the enteric coating base, and 15-30% by weight of various excipients.

In the present invention, although the proton pump inhibitor may also be dissolved and used at the amount of 1-10% by weight relative to the total weight of the

formulation, it is preferably dissolved and used at the amount of 1-4% by weight in view of the stability and expression of optimal effect of the drug. Examples of a suitable solvent which can be used for the dissolution of the proton pump inhibitor include acetone, ethanol, dichloromethane, isopropyl alcohol, purified water and a mixture of two or more thereof. The most preferred solvent is acetone, and it is used at the amount of 30-100 times the proton pump inhibitor, a main drug. If the solvent is used at the amount of less than 30 times the main drug, complete dissolution of the drug cannot be achieved, and if it is used at the amount of more than 100 times, a delay in operation time and the instability of the drug can be caused.

As the alkalizing agent to increase the stability of the proton pump inhibitor, all kinds of alkali substances may be used, but it was confirmed that sodium monohydrogen phosphate, potassium monohydrogen phosphate, sodium hydrogen carbonate, meglumine and ethanolamines are preferred, and mono-, di-, tri-ethanolamine and meglumine are most preferred in the preparation of the inventive double pellet formulation. The alkalizing agent is preferably added in such an amount that the ratio of the proton pump inhibitor : the alkalizing agent is at least about 1:0.1-1:5, and more preferably 1:0.5-1:3. At a ratio of less than 1:0.1, it will not exhibit a function as an alkalizing agent to increase the stability of the proton pump inhibitor, and at a ratio of more than 1:5, the alkalizing agent added will cause a delay in the drying time of a film, resulting in the phenomenon of adhesion between granules or even a lumping phenomenon.

In the present invention, protective coating is

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carried out since the proton pump inhibitor, a main drug, is very unstable in acidic conditions like gastric juice. The protective coating is required to protect the drug against the enteric coating base which is added to ensure the acid stability of the drug. Examples of a protective coating base which can be used in this protective coating include hydroxypropylmethylcellulose and derivatives thereof, polyvinyl alcohol and polyvinyl pyrrolidone. The protective coating base may be used at the amount of about 0.5-4% by weight relative to the total weight of the formulation. At the amount of less than 0.5% by weight, the protective coating base cannot have perfect protective function, and at the amount of more than 4% by weight, it can cause a delay in operation time and a delay in drug dissolution time.

It is most important in the preparation of the inventive double pellet formulation to form an enteric coating layer. This enteric coating layer has a very important effect on the stability of the proton pump inhibitor, an acid-unstable drug, which is contained in the innermost part of the formulation. In the preparation of the inventive double pellet formulation, enteric coating must be performed in such a manner that the enteric coating base may be used at the amount of about 2-7% by weight of the total weight of the formulation. If this enteric coating is performed, an enteric coating layer with a thickness of about 10 μm will be formed on the surface of the formulation. If the enteric coating layer has a thickness of less than 10 μm , the proton pump inhibitor will not show resistance to acidic solution, and if it has a thickness of more than 10 μm , a delay in operation time

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will be caused.

On the outer layer of the enteric-coated formulation, an antibiotic-containing layer is formed such that the antibiotic is preferably contained at the amount of 30-70% by weight relative to the total weight of the formulation.

In the preparation of the inventive double pellet formulation, a GPCG3 fluidized bed processor (Glatt, Germany) was used and similar equipment may also be used to prepare the inventive formulation.

The operation conditions of the fluidized bed processor are adjusted to an inlet air temperature of 50 °C, an outlet air temperature of 40 °C, an air flow rate of 7 m/sec, a nozzle diameter of 1.0 mm, an injection pressure of 1.3 bar and an inlet rate of coating solution of 25 g/min, and then each step was performed.

The present invention will hereinafter be described in further detail by examples. It is to be understood that these examples are presented for illustrative purpose only and not intended to limit the scope of the present invention.

Example 1

Coating with main drug 1

221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of meglumine, an alkalizing agent, is dissolved in 1000 g of acetone, after which 20 g of omeprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug-containing coating solution is

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injected through the fluidized bed coater to coat the sugar particles with the drug.

Protective coating

After performing the main drug coating, a protective
5 coating solution consisting of 20 g of hydroxypropylmethylcellulose and 2 g of polyethylene glycol 600 dissolved in a mixture of 400 g of ethanol and 400 g of dichloromethane is continuously injected onto the main drug-coated pellets to form a protective coating layer.

10 Enteric coating

30 g of Eudragit L100 and 3 g of triethyl citrate are added and dissolved completely in a mixture of 450 g of acetone and 450 g of isopropyl alcohol, and then injected to the protective-coated pellets to form an enteric coating
15 layer.

Coating with main drug 2

500 g of clarithromycin is added and dissolved completely in a mixture of 1000 g of ethanol and 3000 g of dichloromethane, to which 30 g of
20 hydroxypropylmethylcellulose and 3 g of polyethylene glycol 6000 are then added and dissolved, thus preparing a transparent coating solution of the main drug 2. The coating solution is injected onto the enteric-coated pellets to obtain main drug 2-coated pellets.

25 Final coating with film

30 g of hydroxypropylmethylcellulose and 3 g of polyethylene glycol 6000 are added and dissolved in a mixture of 300 g of ethanol and 300 g of dichloromethane, and then coated on the main drug 1- and main drug 2-coated
30 pellets finally, thus preparing a double pellet formulation.

Example 2

Coating with main drug 1

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221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of diethanolamine, an alkalizing agent, is dissolved in 1000 g of acetone, after which 20 g of omeprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Example 3

15 Coating with main drug 1

221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of sodium monohydrogen phosphate is dissolved in 100 g of purified water and then in 900 g of acetone, after which 20 g of omeprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

30 Example 4

Coating with main drug 1

221 g of inert sugar particles are placed into a

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fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of talc is suspended in 1000 g of acetone, after which 20 g of omeprazole is added and dissolved completely in the suspension, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Example 5

Coating with main drug 1

211 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 15 g of meglumine, an alkalizing agent, is dissolved in 1000 g of acetone, after which 30 g of lansoprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Example 6

Coating with main drug 1

211 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 15 g of

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diethanolamine, an alkalizing agent, is dissolved in 1000 g of acetone, after which 30 g of lansoprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 5 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are 10 carried out in the same manner as in Example 1.

Example 7

Coating with main drug 1

211 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated 15 to fluidize the particles to be coated. Meanwhile, 15 g of sodium monohydrogen phosphate is dissolved in 150 g of purified water and then in 900 g of acetone, after which 30 g of lansoprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g 20 of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

25 A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Example 8

Coating with main drug 1

211 g of inert sugar particles are placed into a 30 fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of talc is suspended in 1000 g of acetone, after which 30 g of

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lansoprazole is added and dissolved completely in the suspension, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-
5 containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

10 Example 9Coating with main drug 1

221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of
15 meglumine, an alkalizing agent, is dissolved in 1000 g of acetone, after which 20 g of pantoprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution.
20 The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

25 Example 10Coating with main drug 1

221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of
30 diethanolamine, an alkalizing agent, is dissolved in 1000 g of acetone, after which 20 g of pantoprazole is added and dissolved completely in the solution, and then 25 g of

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hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Example 11

Coating with main drug 1

221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of sodium monohydrogen phosphate is dissolved in 100 g of purified water and then in 900 g of acetone, after which 20 g of pantoprazole is added and dissolved completely in the solution, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Example 12

Coating with main drug 1

221 g of inert sugar particles are placed into a fluidized bed processor, and then the processor is operated to fluidize the particles to be coated. Meanwhile, 10 g of talc is suspended in 1000 g of acetone, after which 20 g of pantoprazole is added and dissolved completely in the suspension, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved

completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

- 5 A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Comparative Example 1

Coating with main drug 1

- 231 g of inert sugar particles are placed into a
10 fluidized bed processor, and the processor is operated to fluidize the particles to be coated. Meanwhile, 20 g of omeprazole is added and dissolved completely in 1000 g of acetone, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved
15 completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

- A protective coating step and subsequent steps are
20 carried out in the same manner as in Example 1.

Comparative Example 2

Coating with main drug 1

- 221 g of inert sugar particles are placed into a fluidized bed processor, and the processor is operated to
25 fluidize the particles to be coated. Meanwhile, 30 g of lansoprazole is added and dissolved completely in 1000 g of acetone, and then 25 g of hydroxypropylcellulose and 2.5 g of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-
30 containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

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A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

Comparative Example 3

Coating with main drug 1

5 231 g of inert sugar particles are placed into a fluidized bed processor, and the processor is operated to fluidize the particles to be coated. Meanwhile, 20 g of pantoprazole is added and dissolved completely in 1000 g of acetone, and then 25 g of hydroxypropylcellulose and 2.5 g
10 of polyethylene glycol 6000 are added and dissolved completely in the solution. The resulting main drug 1-containing coating solution is injected through the fluidized bed coater to coat the sugar particles with the drug.

15 A protective coating step and subsequent steps are carried out in the same manner as in Example 1.

20 Test Example 1: Stability test and comparative evaluation of omeprazole/clarithromycin composite formulation

		Example 1	Example 2	Example 3	Example 4	Comparative Example 1
Change in appearance		No change	No change	No change	No change	Browning
Change in content (at 40°C and 75% RH)	1 month	100.1/101.0	100.4/100.9	100.1/101.7	100.0/101.0	77/100.1
	3 months	100.2/100.8	101.1/101.2	100.0/101.4	99.3/100.3	60/100.2
	6 months	100.1/100.8	100.5/101.6	100.3/101.0	98.7/101.2	43/100.1

*Change in content: omeprazole content/clarithromycin content

Test example 2: Stability test and comparative evaluation of lansoprazole/clarithromycin composite formulation

		Example 5	Example 6	Example 7	Example 8	Comparative Example 2
Change in appearance		No change	No change	No change	No change	Browning
Change in content (at 40°C and 75% RH)	1 month	99.9/101.0	101.1/100.9	99.5/101.7	93.2/101.0	63.8/101.2
	3 months	100.1/100.3	100.9/100.6	99.9/101.4	89.3/100.3	45.7/100.5
	6 months	100.0/101.1	100.2/100.5	100.2/101.0	90.1/101.2	39.4/100.2

*Change in content: lansoprazole content/clarithromycin

5 content

Test Example 3: Stability test and comparative evaluation of pantoprazole/clarithromycin composite formulation

		Example 9	Example 10	Example 11	Example 12	Comparative Example 3
Change in appearance		No change	No change	No change	No change	Browning
Change in content (at 40°C and 75% RH)	1 month	100.3/100.6	100.2/101.9	100.8/100.8	78.0/101.2	68.0/100.2
	3 months	100.6/100.3	100.5/101.4	101.1/100.2	53.3/100.8	38.5/100.6
	6 months	100.1/101.2	100.1/100.3	100.4/100.6	38.6/100.2	29.4/100.5

*Change in content: Pantoprazole content/clarithromycin

10 content

Test Example 4: Dissolution test of formulation

		Example 1	Example 2	Example 5	Example 9	Comparative Example 1
Just after preparation		98.2/99.7	99.4/99.5	99.3/98.9	99.8/98.5	56.3/97.2
Change in content (at 40°C and 75% RH)	1 month	97.7/99.7	98.3/97.9	96.3/98.2	96.5/97.7	38.3/98.5
	3 months	96.2/98.9	96.4/98.8	97.2/98.4	94.9/98.1	22.5/98.1
	6 months	95.8/97.9	96.1/98.1	95.3/99.1	96.8/98.5	20.1/97.4

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120**Industrial Applicability**

As described above, the present invention provides the double pellet formulation in which layers separated from each other are formed in one pellet, and a proton pump inhibitor and antibiotic clarithromycin are contained in the separated layers, respectively, such that upon administration of the formulation, the drugs can be released in different sites of the living body in a more stable form, thus maximizing a therapeutic effect against various peptic ulcers, including a peptic ulcer caused by *Helicobacter pylori*.

Furthermore, the present invention provides a simple posology for the administration of two or more active ingredients. In addition, the present invention provides a double pellet formulation effective for the treatment of various peptic ulcers, including a peptic ulcer caused by *Helicobacter pylori*, which allows active ingredients to be activated at suitable time intervals and suitable amounts, thus preventing the interaction between the active ingredients, as well as a preparing method thereof.

What Is Claimed Is:

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1. A method for preparing a double pellet formulation with a spherical pellet shape, the method comprising the
5 steps of:

dissolving a proton pump inhibitor and an alkalizing agent together with a coating base in a solvent, to prepare a coating solution;

10 coating an inert sugar particle with the coating solution;

subjecting the coated sugar particle to protective coating and then to enteric coating, to prepare a formulation capable of protecting the proton pump inhibitor, an acid-unstable drug; and

15 coating the outer layer of the enteric coated particle with an antibiotic together with a coating base.

2. A method for preparing a double pellet formulation with a spherical pellet shape, the method comprising the
20 steps of:

dissolving 1-4% by weight, based on the total weight of the formulation, of a proton pump inhibitor and 0.1-7% by weight of an alkalizing agent, together with a coating base in a solvent, to prepare a coating solution;

25 coating 15-30% by weight of an inert sugar particle with the coating solution;

subjecting the coated sugar particle to protective coating and then to enteric coating, to prepare a formulation capable of protecting the proton pump inhibitor, an acid-unstable drug; and
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coating the outer layer of the enteric-coated particle with 30-70% by weight of an antibiotic together

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with a coating base.

3. The method of Claim 1 or 2, wherein the proton pump inhibitor is selected from the group consisting of
5 omeprazole, lansoprazole, pantoprazole and rabeprazole.

4. The method of Claim 1 or 2, wherein the alkalizing agent is selected from the group consisting of meglumine, eglumine, diethanolamine, monoethanolamine, triethanolamine,
10 talc, magnesium hydroxide, magnesium oxide, sodium monohydrogen phosphate, potassium monohydrogen phosphate, arginine, lysine, histidine, and a mixture of two thereof.

5. The method of Claim 1 or 2, wherein a protective
15 coating base used in the protective coating step is selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, and a mixture of two thereof.

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6. The method of Claim 1 or 2, wherein an enteric coating base used in the enteric coating step is selected from the group consisting of methacrylic acid copolymer, cellulose acetate phthalate, cellulose acetate butylate,
25 hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylcellulose, shellac and a mixture of two thereof.

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7. The method of Claim 1 or 2, wherein the antibiotic is selected from the group consisting of a macrolide

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antibiotic, an imidazole antibiotic, a tetracycline antibiotic and a mixture of two thereof.

8. The method of Claim 7, wherein the macrolide
5 antibiotic is selected from the group consisting of erythromycin, clarithromycin, azithromycin, and roxithromycin.

9. The method of Claim 7, wherein the imidazole
10 antibiotic is selected from the group consisting of metronidazole, apronidazole, azomycin, benzonidazole, carnidazole, demetridazole, etanidazole, flunidazole, misonidazole, nimorazole, ornidazole, panidazole, ronidazole, and tinidazole.

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10. The method of Claim 7, wherein the tetracycline antibiotic is selected from the group consisting of tetracycline, chlorotetracycline, doxycycline, glycocycline, guamecycline, lymecycline, metacycline, and sancycline.

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11. A double pellet formulation prepared by the method of any one of Claims 1 to 10.