



No. 13-111735- -00002-0000

Fecha: 2013-09-25 16:44:16 Dep. 2020 DIR.NUEVASCR
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DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

☒ Patente de invención

☐ Registro de Diseño Industrial

☐ Patente de Modelo de Utilidad

Esquema de Trazado de Circuitos Integrados

Número de expediente: 13-111-735

Solicitante: SAMSUNG FINE CHEMICALS CO., LTD.

Apoderado: JUAN PABLO CADENA SARMIENTO

Título de la Nueva Creación: COMPOSICION PARA CAPSULAS DURAS ENTERICAS, Y CAPSULA SURA(sic) ENTERICA PREPARADA USANDO LA COMPOSICION.

Gaceta: 670 de 28 de junio de 2013, No. de publicación 869.

2. Datos del Opositor

Persona Natural

Persona Jurídica

C.I. FARMACAPSULAS S.A.

Nombre o denominación /Razón social completa

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otro ☐Cuál

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Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

REYES VILLAMIZAR JOSE LUIS

79 152.473

44655

Apellidos y Nombre

Documento de identificación

T.P. No.

Dirección del representante

Cra 17 No. 88-23 Of.205

Dirección electrónica

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Número telefónico

621.26.31

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación

6. Fundamentos de la oposición

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000)

Justificación: VER ANEXO

Prórroga: SI ☒ NO ☐

7. Anexos

☒ Comprobante de pago de la tasa para la presentación de la solicitud No. _____ Fecha: _____

☒ Poder, si fuera el caso con el que se acredita la representación.

☒ Pruebas de los fundamentos de la oposición

☒ Copias para traslado

8. Firma

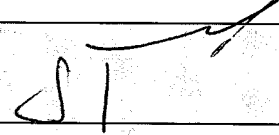
JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos

Firma

79.152.473

C.C.



44655

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

EXPEDIENTE 13-111-735

TÍTULO SOLICITADO:

“COMPOSICIÓN PARA CÁPSULAS DURAS
ENTÉRICAS Y CÁPSULA SURA (sic) ENTÉRICA
PREPARADA USANDO LA COMPOSICIÓN”

PUBLICACIÓN:

Gaceta 670 de 28 de junio de 2013, N° de
publicación 869.

PRIORIDAD:

KO (sic) 10-2010-0103053 21/10/2010

SOLICITANTE:

SAMSUNG FINE CHEMICALS CO., LTD.

APODERADO:

JUAN PABLO CADENA SARMIENTO

TRÁMITE:

PRESENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **C.I. FARMACAPSULAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000 y demás normas concordantes, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **13-111-735**, por no cumplir con lo dispuesto en la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **C.I. FARMACÁPSULAS S.A.** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite 13-111-735, referida a una composición para cápsulas duras entéricas y una cápsula dura entérica preparada usando la composición, donde dicha composición para cápsulas duras entéricas puede incluir un poliol, el cual tiene por lo menos tres grupos hidroxilo, no reúne los requisitos necesarios para el otorgamiento de privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

1. Falta de claridad, sustento y concisión en las reivindicaciones y descripción.

En primer término, debo anotar que las reivindicaciones son imprecisas y no reflejan lo descrito en el cuerpo del documento, en tanto se refieren a rangos imprecisos y amplios que no permitirían a una persona medianamente versada en la materia técnica, derivar la composición deseada. Así mismo, las reivindicaciones tampoco permiten identificar las composiciones que cumplen con los parámetros definidos y que aportan la pretendida ventaja técnica, haciendo que la materia reivindicada resulte vaga y especulativa, en contravención de las normas que imponen a las solicitudes de patente claridad y concisión.

De otro lado, se llama la atención a que las reivindicaciones incluyen expresiones y términos que no son claros, y que abarcan materia no desarrollada ni ejemplificada en el capítulo descriptivo, hecho que dificulta la adecuada comparación frente al estado de la técnica, pues reivindica múltiples ideas

generales, carentes de cualquier sustentación en la memoria descriptiva, y por supuesto, de demostración práctica alguna. Una simple revisión de la reivindicación 1 permite ejemplificar lo expuesto:

[Reivindicación 1]

Una composición para las cápsulas duras entéricas, comprendiendo la composición:

alrededor de 50 partes a alrededor de 90 partes en peso de ftalato de hidroxipropilmetilcelulosa (HPMCP);

alrededor de 10 partes alrededor de 50 partes en peso de hidroxipropil metilcelulosa (HPMC);

alrededor de 5,5 alrededor de 8,5 partes en peso de un agente alcalino; y

alrededor de 2 partes a alrededor de 15 partes en peso de poliol, el cual tiene por lo menos tres grupos hidroxilo,

en donde las cantidades de la HPMCP, la HPMC, el agente alcalino y el poliol en partes en peso se basan en 100 partes en peso del peso total de la HPMCP y la HPMC.

De la lectura de la reivindicación 1, se colige que la composición pretendida incluye un número indeterminado de proporciones de los 4 ingredientes empleados (HPMCP, HPMC; agente alcalino, poliol), que pueden variar entre límites igualmente indefinidos basados en la expresión "alrededor", lo que impide conocer con la debida claridad los límites de las proporciones reclamadas. Por ello, deberá concluirse que las reivindicaciones, en especial la reivindicación 1, principal, incumple con los requisitos de claridad y concisión.

En adición a lo anterior, la citada reivindicación principal no define técnicamente los compuestos de la composición, en tanto hace referencia a "el agente alcalino y el poliol", que son simplemente mencionados por su función y/o grupo funcional, técnica que impide identificar debidamente los componentes de la formulación de interés.

De otro lado, se llama la atención del Despacho al hecho de que la solicitud en mención – en la reivindicación dependiente 2 - reclama además una composición de ftalato de hidroxipropilmetilcelulosa caracterizada por sus componentes y su

proporción dentro de la misma, y se resalta el hecho de que dicha composición está comprendida en la composición principalmente reclamada, veamos:

[Reivindicación 2]

La composición de la Reivindicación 1, en donde el HPMCP incluye alrededor de 20% en peso a alrededor de 24% en peso de un grupo metoxi, alrededor de 6% en peso a alrededor de 10% en peso de un grupo hidroxipropoxi, y alrededor de 21% en peso a alrededor de 26% en peso de un grupo ftalilo, y tiene una viscosidad cinética de alrededor de 48 cSt a alrededor de 66 cSt.

Como se puede entender de la lectura de la reivindicación 2, efectivamente el término HPMCP – que según la reivindicación principal el componente está presente en la composición de cápsulas de alrededor de 50 partes a alrededor de 90 partes en peso de ftalato de hidroxipropilmetilcelulosa – corresponde a otra composición con sus propios ingredientes:

- grupo metoxi, de aproximadamente 20 a 24 % en peso
- grupo hidroxipropoxi, de aproximadamente 6 a 10 % en peso
- grupo ftalilo, de aproximadamente 21 a 26% en peso.

De lo anteriormente expuesto, deberá concluirse que los componentes de esta segunda composición no han sido allí identificados, así como tampoco lo han sido las proporciones allí mencionadas, de forma que **la reivindicación 2 en lugar de restringir o precisar el alcance de la reivindicación 1, como en derecho correspondería, lo que hace es aumentarlo, lo que la hace técnicamente inaceptable.**

Además, en el caso de la reivindicación 2, se pretende reclamar la composición de HPMCP mediante la viscosidad cinética, lo cual no es claro y constituye una redacción basada en un “resultado a alcanzar”, que en ningún momento define en forma debida una composición. Por lo tanto, se concluye que la materia de la reivindicación 2 carece de claridad y hace más confusa y difícil de entender a la materia divulgada en la reivindicación principal.

En general, las reivindicaciones dependientes, aunque hacen referencia a las anteriores, incluyen componentes que no permiten definir el objeto inventivo, en

tanto, además de los cuatro componentes esenciales inicialmente planteados, se incluyen otros como emulsificantes tales como lauril sulfato sódico, éster de azúcar y mezclas de los anteriores, como en el caso de la reivindicación 6:

[Reivindicación 6]

La composición de la Reivindicación 5, en donde el emulsionador comprende por lo menos uno seleccionado del grupo conformado por lauril sulfato sódico (SLS), éster de azúcar (SE), y una mezcla de por lo menos dos de los anteriores.

A pesar de que las reivindicaciones dependientes mencionan una selección de los posibles componentes y agentes funcionales en la composición, la composición tal y como fue reclamada continúa siendo solo una serie de posibles composiciones que varía entre una selección de múltiples componentes, bajo cantidades que también varían de forma desproporcionada, circunstancia que permite concluir, una vez más, que la solicitud carece de concisión en sus reclamaciones.

2. Problema técnico que resuelve la presente solicitud

La presente solicitud 13-111-735 plantea la necesidad de derivar un producto que no presente los problemas de las composiciones de cápsulas convencionales, como su baja transparencia y su fragilidad frente a un contenido de humedad de 10% en peso o menos.

Además, el solicitante desea proveer una nueva composición que supere los problemas que aparecen al almacenar dicha cápsulas en condiciones de alta temperatura severas ya que las cápsulas HPMCP pueden perder humedad en el interior y se endurecen lentamente, pues incluyen un exceso de un agente neutralizante (por ejemplo, agente alcalino).

Por otra parte, en las cápsulas convencionales el agente neutralizante puede separarse de las cápsulas endurecidas, lo que también se llama una separación de la sal, en un período relativamente corto de tiempo, sobre todo dentro de 30 días.

Para resolver dichos problemas, la solicitud en trámite reclama una composición para cápsulas duras entéricas, que incluye ftalato de hidroxipropilmetilcelulosa

(HPMCP); hidroxipropil metilcelulosa (HPMC); un agente alcalino, y un poliol que tiene al menos tres grupos hidroxilo.

3. La solicitud no cumple con los requisitos de novedad y nivel inventivo.

Sin perjuicio de reiterar que la solicitud no cumple siquiera con los requisitos formales, es oportuno, desde ahora, anotar que existen en el estado de la técnica documentos que ya han reclamado la misma materia bajo la composición empleada, y que permiten sin lugar a dudas, la resolución del mismo problema técnico, tal como sucede con la patente americana US 6346269 publicada por Fang-Hsiung Hsiao, en adelante Fang et al., titulado "*Method for preparing an oral formulation containing acid-sensitive drugs and oral formulation made thereby*" del 12 de febrero de 2002.

Dicho documento menciona cada una de las características técnicas esenciales de la solicitud en trámite, al describir una formulación oral que comprende fialato de hidroxipropil metil celulosa (MPMCP), hidroxiproil metil celulosa (HPMC), al menos un agente alcalino y estabilizadores, tal como se puede observar en el resumen del documento:

(57)

ABSTRACT

The present invention relates to a method for preparing an oral formulation containing acid-sensitive drugs, including at least the following step: spreading a solution or a suspension containing at least stabilizers, solvents and acid-sensitive drugs or its pharmaceutically acceptable salts onto a core made from one or more excipients, and then drying the core to make an active ingredient layer over the core. Also disclosed is the oral formulation made by this method.

En el citado documento, también se incluyen métodos para producir composiciones orales y entéricas que comprenden el ingrediente activo con envolturas entéricas:

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ing acid-sensitive drugs in the shape of a pellet that is circular in cross section and contains, from inside to outside, a core (1), an active ingredient-containing layer (2), a sub-coating layer (3) and an enteric coating layer (4). In addition, one or more active ingredient containing-layers (2) 5 containing active ingredient and/or one or more sub-coating layers (3) can be applied between the core (1) and the enteric coating layer (4).

Los adhesivos seleccionados se encuentran en la técnica dando lugar a que la composición de la solicitud en trámite sea una selección de los compuestos descritos en la anterioridad citada, veamos:

Optionally, one or more adhesives can be added to prepare the core, which are selected from the group consisting of polyvinyl pyrrolidone (PVP), gelatin, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), vinyl acetate (VA), polyvinyl alcohol (PVA), methyl cellulose (MC), ethyl cellulose (EC), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalates (CAP), xanthan gum, alginic acid,
40 salts of alginic acid, Eudragit®, copolymer of methyl acrylic acid/methyl methacrylate with polyvinyl acetate phthalate (PVAP).

Adicionalmente, los polioles se describen tal como se observa en el estado de la técnica así:

Optionally, one or more plasticizers can be further added to prepare the core. Suitable plasticizers are selected from
50 the group consisting of glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.

Los agentes alcalinos también son incluidos en la preparación de la composición revelada en la anterioridad tantas veces mencionada:

25 Procedure:
10 g of PEG 6000, 16 g of HPC and 800 ml of pure water were mixed together to prepare an aqueous solution.
Then, 1.4 g of dibasic sodium phosphate and 1.4 g of
30 tribasic sodium phosphate were poured and mixed into the prepared aqueous solution.

Los emulsificantes empleados por la solicitud en trámite, han sido también contemplados en el estado de la técnica tal como se observa en el siguiente aparte:

In step (a), the core (1) can be prepared in advance or can be prepared in situ after forming the solution or suspension containing the acid-sensitive drugs or its pharmaceutically acceptable salts and the solvents with the stabilizers. Therefore in one embodiment of the method in accordance with
45 the present invention, the method is started by preparing a solution or a suspension by mixing the stabilizers with the solvents.

De acuerdo con lo anterior, se observa que la composición reclamada ya era conocida y había sido divulgada por un documento de patente anterior, haciendo que la materia en mención no pueda ser reclamada nuevamente, hecho que debería ser suficiente para negar de plano la presente solicitud de patente. En este caso, al estar todos los componentes presentes en la solicitud y dadas las faltas en claridad, la solicitud no cumple con el requisito de novedad.

Por otra parte, y tal como ya se ha mencionado al inicio del presente documento, la solicitud señala intervalos de concentración tan amplios que permiten que el técnico versado en la materia incluya los componentes de la composición para cápsulas entéricas en las proporciones deseadas para lograr los efectos deseados; en vista de que dichas proporciones son habituales en el estado de la técnica, lo reclamado por la solicitud no cumple con los requisitos de nivel inventivo.

Por último, teniendo en cuenta el efecto ventajoso de la solicitud 13-111-735, el cual consiste en la provisión de cápsulas duras entéricas altamente transparentes, mecánicamente fuertes, con una separación retrasada de sal de las mismas durante el almacenamiento, éste había sido logrado en la técnica al reducir la actividad de la cápsula con el principio activo tal y como se observa en el documento de anterioridad en la columna 1:

Owing to the stability of omeprazole, omeprazole should not contact gastric acid solution after administering the total formulation containing omeprazole, since the gastric acid solution will lower the activity of the omeprazole. Therefore, the oral formulation containing omeprazole is usually treated with an enteric coating to prevent the omeprazole from direct contact with the gastric acid solution. However, the enteric coating is usually made with acidic chemicals, thus when the oral formulation containing omeprazole is directly treated with the enteric coating, the omeprazole will rapidly decompose due to direct or indirect contact with the acidic ingredient in the enteric coating, such that the oral formulation will be discolored and the activity will be reduced during storage.

Por lo tanto, el efecto técnico que presenta la solicitud colombiana 13-111-735 no es inventivo pues no aporta una solución sorprendente o inesperada, y más aún, una persona medianamente versada en la materia sabría que la combinación de los agentes de encapsulamiento, plastificantes, emulsificantes y estabilizantes

empleados en la formulación de la cápsula eran ya conocidos para el momento de la presentación de la solicitud.

Se concluye, entonces, que la composición reclamada por el solicitante carece de altura inventiva.

Por lo tanto, con los argumentos dados en el presente escrito, un técnico medio en la materia habría fácilmente derivado la materia de la solicitud bajo una selección de las características técnicas sugeridas presentaban los conocimientos y datos necesarios para que el experto medio en la materia llegara al objeto reclamado.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Patente americana US 6346269 publicada por Fang-Hsiung Hsiao, titulada *"Method for preparing an oral formulation containing acid-sensitive drugs and oral formulation made thereby"* del 12 de febrero de 2002. Todo el documento.

VII. ANEXOS

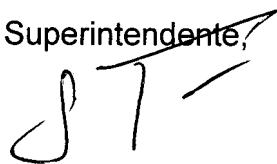
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de C.I. FARMACÁPSULAS S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere
5. Copia para correr traslado al solicitante.
6. Las mencionadas en el acápite de pruebas

VIII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.



US006346269B1

(12) **United States Patent**
Hsiao et al.

(10) Patent No.: **US 6,346,269 B1**
(45) Date of Patent: **Feb. 12, 2002**

(54) **METHOD FOR PREPARING AN ORAL FORMULATION CONTAINING ACID-SENSITIVE DRUGS AND ORAL FORMULATION MADE THEREBY**

(75) Inventors: **Fang-Hsiung Hsiao; Chien-Chu Lin,**
both of Tainan Hsien; **Ya-Ching Changchien,** Kaohsiung, all of (TW)

(73) Assignee: **Standard Chem. & Pharm. Co., Ltd.,**
Tainan (TW)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/567,083**

(22) Filed: **May 8, 2000**

(51) Int. Cl.⁷ **A61K 9/24; A61K 9/20;**
A61K 9/48; A61K 9/54

(52) U.S. Cl. **424/472; 424/464; 424/465;**
424/451; 424/458

(58) Field of Search **424/464, 465,**
424/458, 451, 472

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,385,739 A * 1/1995 Debregeas et al. 424/494
5,540,945 A * 7/1996 Ikushima 424/490

* cited by examiner

Primary Examiner—Thurman K. Page

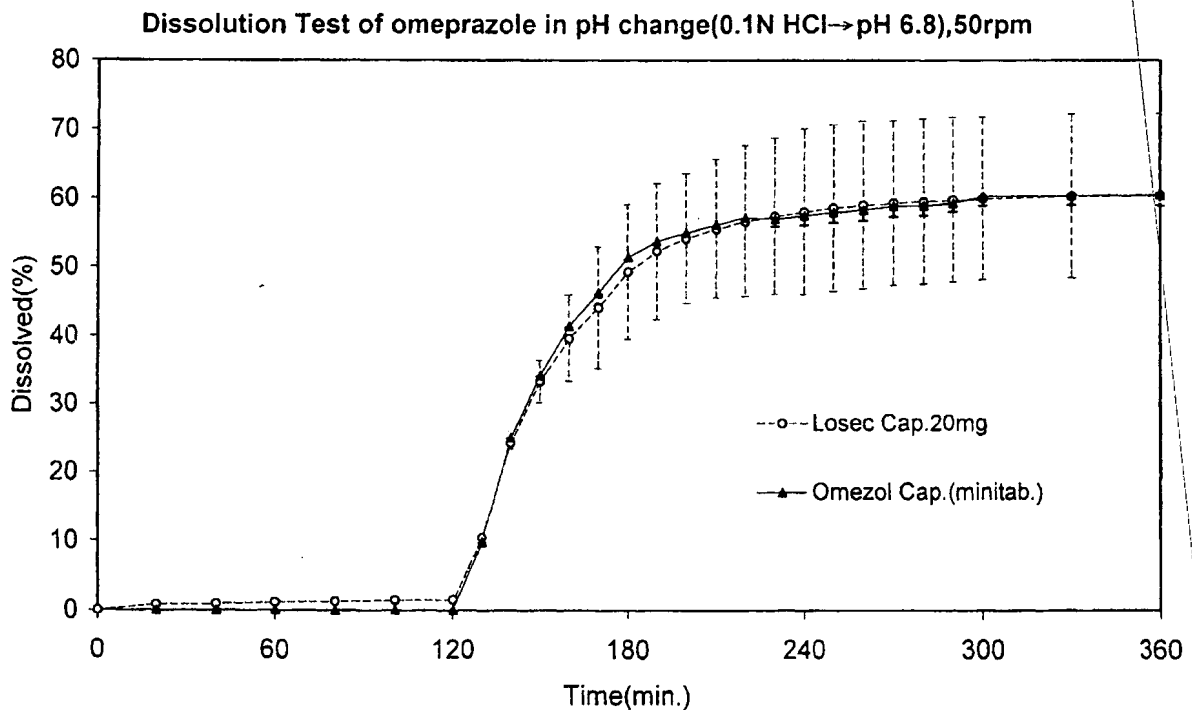
Assistant Examiner—Rachel M. Bennett

(74) *Attorney, Agent, or Firm*—Rosenberg, Klein & Lee

(57) **ABSTRACT**

The present invention relates to a method for preparing an oral formulation containing acid-sensitive drugs, including at least the following step: spreading a solution or a suspension containing at least stabilizers, solvents and acid-sensitive drugs or its pharmaceutically acceptable salts onto a core made from one or more excipients, and then drying the core to make an active ingredient layer over the core. Also disclosed is the oral formulation made by this method.

28 Claims, 4 Drawing Sheets



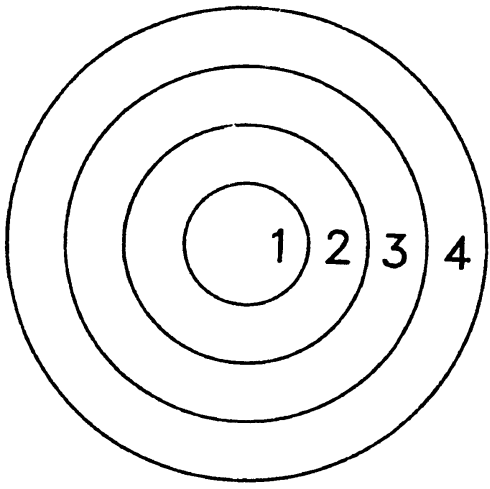


FIG.1

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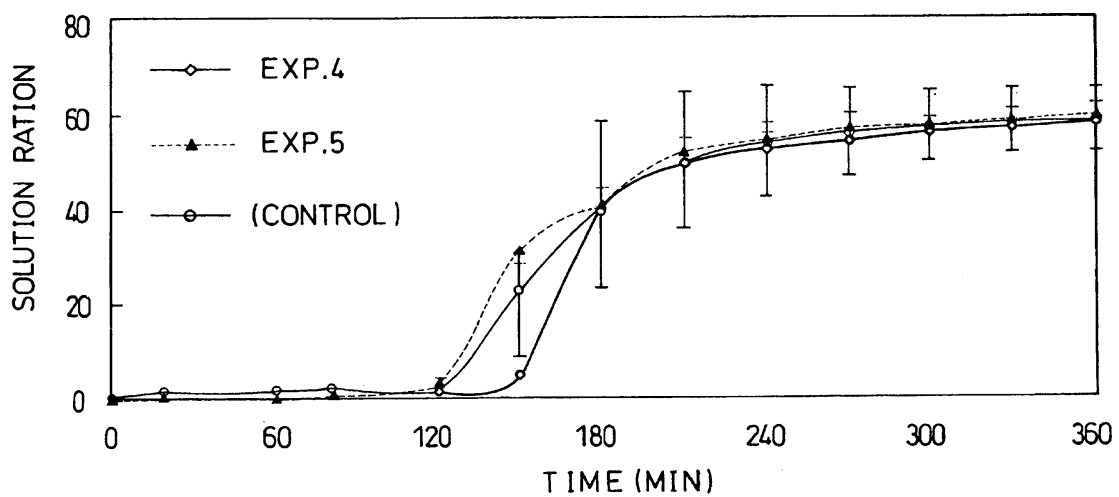
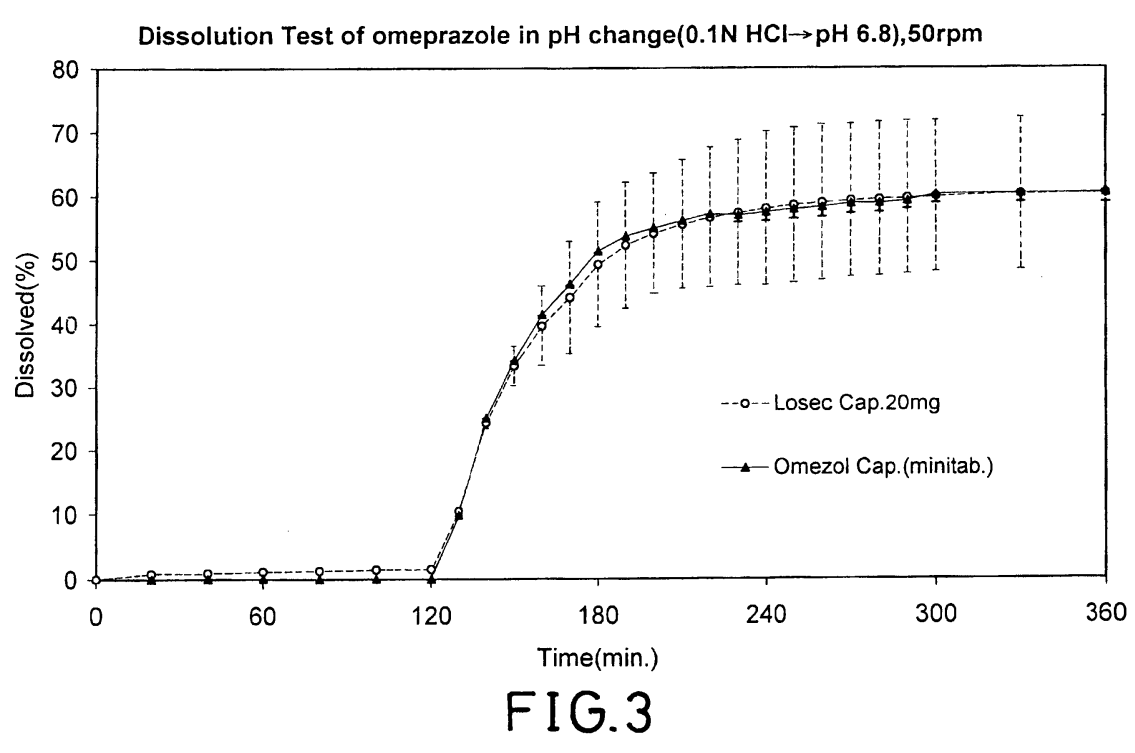


FIG.2



16

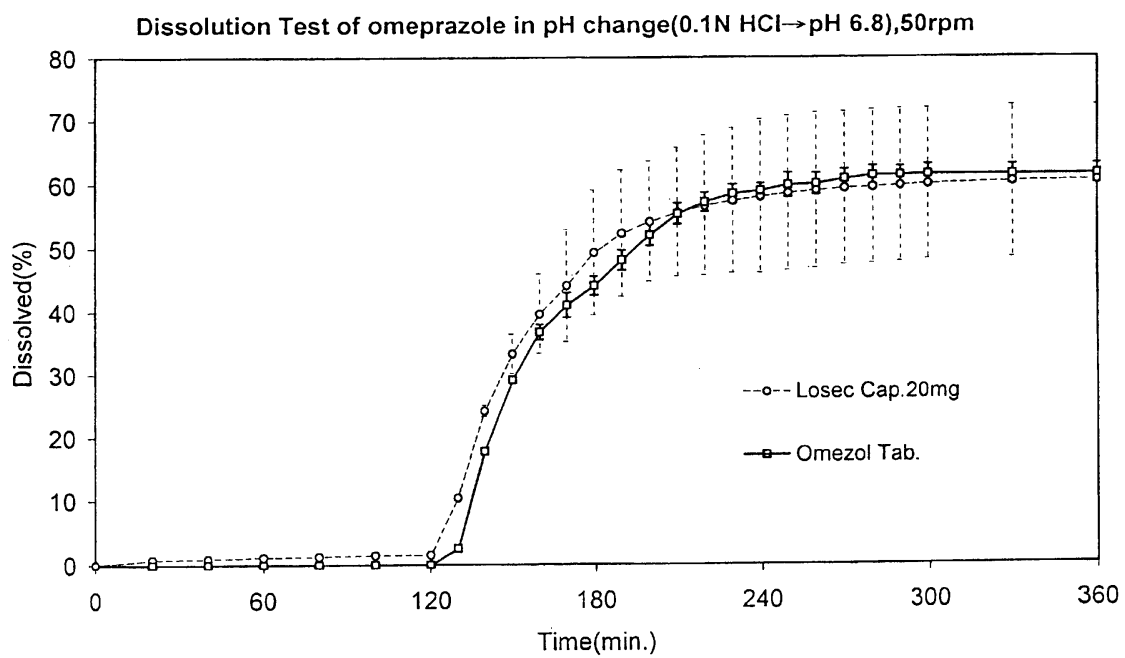


FIG.4

1

METHOD FOR PREPARING AN ORAL FORMULATION CONTAINING ACID-SENSITIVE DRUGS AND ORAL FORMULATION MADE THEREBY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method for preparing an oral formulation containing acid-sensitive drugs, and especially to a method for preparing an oral formulation containing omeprazole having an layer of evenly distributed omeprazole coated on the core.

2. Description of Related Art

The acid-sensitive drugs essentially comprise substituted benzimidazole gastric anti-secretary agent such as omeprazole, lansoprazole, pantoprazole and pharmaceutically acceptable salts thereof. These agents are well-known strong inhibitors for inhibiting gastric acid secretion in mammals. The acid-sensitive drugs have irreversible inhibiting-action against the enzymatic system of H/K ATPase in the human body. In other words, they can inhibit the proton pumps of the gastroparietal cells. However, it is easy for the acid-sensitive drugs to decay in an acidic environment to become non-active ingredients. Therefore, there is a need in the field of the active ingredient manufacturing to overcome the above-mentioned problem.

For example, omeprazole is very unstable in an acidic environment. The half-life of degradation of omeprazole in water solutions at pH-values less than four is shorter than ten minutes. Even at neutral pH-values degradation proceeds rapidly, e.g. at pH=7 the half-life of omeprazole is about 14 hours. Therefore, omeprazole cannot exist in an acidic environment. The stability of omeprazole is also affected by moisture, heat, and organic solvents and to some degree by light. It is reported in some literature that omeprazole possesses acceptable stability in a base environment.

Owing to the stability of omeprazole, omeprazole should not contact gastric acid solution after administering the total formulation containing omeprazole, since the gastric acid solution will lower the activity of the omeprazole. Therefore, the oral formulation containing omeprazole is usually treated with an enteric coating to prevent the omeprazole from direct contact with the gastric acid solution. However, the enteric coating is usually made with acidic chemicals, thus when the oral formulation containing omeprazole is directly treated with the enteric coating, the omeprazole will rapidly decompose due to direct or indirect contact with the acidic ingredient in the enteric coating, such that the oral formulation will be discolored and the activity will be reduced during storage.

One conventional method for preparing an oral formulation containing omeprazole is proposed to overcome the above-mentioned problem. This conventional method consists of stabilizing the omeprazole by putting the omeprazole and a part of the excipients into an ammonia-containing environment instead of utilizing the base core consisting of omeprazole and base chemicals, and then spreading solutions onto the core with an eccentric separator while adding a globing agent from a supply funnel to form pellets containing the active ingredients.

However, the above-mentioned conventional method includes adding a globing agent at any time during preparing the pellets of the oral formulations. Such an addition of globing agent during the preparation of the pellets is very inconvenient in a process for preparing a pellet, and causes

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variable sizes of pellets resulting in a greater difference in terms of releasing rate of the oral formulation. Therefore, this conventional method is not acceptable to manufactures seeking a preparation method that is operated easily and can produce an homogeneously distributed oral preparation. In addition, the ammonia used in this conventional method also causes a problem of noxious fumes at the preparation site and is not environmentally friendly.

Therefore, there is still a need to provide a method for preparing an oral formulation with acid-sensitive drugs which solves the problem of the difference in pellet size and enhances the consistency of the releasing rate.

SUMMARY OF THE INVENTION

The objective of the present invention is to provide a method for preparing an oral formulation containing acid-sensitive drugs having a layer of evenly distributed active ingredient coated on the core.

To achieve the objective, the method in accordance with the present invention comprises:

- (a) spreading a solution or a suspension comprising stabilizers, solvents and acid-sensitive drugs or its pharmaceutically acceptable salts onto a core made from one or more excipients, and then drying the spread core to make a core with an active ingredient layer;
- (b) spreading a solution or suspension comprising adhesives, plasticizer, anti-tackiness and solvents on the active ingredient layer containing the core achieved in (a) and then drying the solution or suspension to form a sub-coating layer over the active ingredient layer; and
- (c) spreading a suspension comprising enteric-soluble coating material, plasticizer, anti-tackiness agent and solvents onto the sub-coating layer achieved in (b) and then drying the spread suspension to make an enteric coating layer over the sub-coating layer. With the method in accordance with the present invention, the oral formulation containing acid-sensitive drugs has a layer of evenly distributed active ingredient layer coated on the core without active ingredients.

Other objectives, advantages and novel features of the invention will become more apparent from the following detailed description when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-sectional plan view of one embodiment of the oral formulation containing acid-sensitive drugs in accordance with the present invention;

FIG. 2 is a graph showing the active ingredient-dissolution rates of the oral formulations each containing acid-sensitive drugs made by the present invention and prior art;

FIG. 3 is a graph showing the active ingredient-releasing rates of the oral formulations each containing acid-sensitive drugs made by the present invention and prior art; and

FIG. 4 is a graph showing the active ingredient-releasing rates of the oral formulations each containing acid-sensitive drugs made by the present invention and prior art.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

With reference to FIG. 1, the method in accordance with the present invention provides the oral formulation contain-

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ing acid-sensitive drugs in the shape of a pellet that is circular in cross section and contains, from inside to outside, a core (1), an active ingredient-containing layer (2), a sub-coating layer (3) and an enteric coating layer (4). In addition, one or more active ingredient containing-layers (2) containing active ingredient and/or one or more sub-coating layers (3) can be applied between the core (1) and the enteric coating layer (4).

Although the preferred oral formulation is circular in cross-section, other suitable shape such as a granule, a tablet, a mini-tablet (the term "mini" means a size of from 3 mm to 5 mm) can be employed in the present invention.

Optionally, more than one layer (2) containing active ingredient and/or sub-coating layer (3) can be formed between the core (1) and the enteric coating layer (4). The prepared oral formulation can further be, either alone or together with other excipients, made into a active ingredient having a pharmaceutical amount of the oral formulation containing acid-sensitive drugs. For example it can be filled into a capsule or compressed into a tablet or a pellet.

The pellet shown in FIG. 1 is produced by the method in accordance with the present invention comprising the following steps:

- (a) spreading a solution or a suspension comprising stabilizers, solvents and acid-sensitive drugs or its pharmaceutically acceptable salts onto a core made from one or more excipients, and then drying the spread core to make a core coated with an active ingredient layer;
- (b) spreading a composition solution or suspension comprising adhesives, plasticizer, anti-tackiness and solvents on the active ingredient layer containing the core achieved in (a) and then drying the solution or suspension to form a sub-coating layer over the active ingredient layer; and
- (c) spreading a suspension comprising enteric-soluble coating material and solvents onto the sub-coating layer achieved in (b) and then drying it to make an enteric coating layer over the sub-coating layer.

Details for each step will be described in the following.

In step (a), the core (1) can be prepared in advance or can be prepared in situ after forming the solution or suspension containing the acid-sensitive drugs or its pharmaceutically acceptable salts and the solvents with the stabilizers. Therefore in one embodiment of the method in accordance with the present invention, the method is started by preparing a solution or a suspension by mixing the stabilizers with the solvents.

The suitable solvents useful for the solution or suspension in the method in accordance with the present invention can be one member selected from the group consisting of water, alcohols, acetone, isopropanol, dichloromethane and compositions thereof. The preferable solvent includes ethanol, acetone and isopropanol.

The suitable stabilizers useful for the solution or suspension in step (a) of the method in accordance with the present invention can be a member selected from the group consisting of hydroxides of alkali-metals and alkaline earth metals, bases of phosphates and organic acid salts and organic amines.

Subsequently, anti-tackiness and acid-sensitive drugs or its pharmaceutically acceptable salts are added to the solution or suspension to prepare a solution or suspension containing the active ingredient. Optionally, other agents such as adhesives, plasticizers or other diluents can be further added to the solution or suspension. Suitable anti-tackiness are selected from the group consisting of talc,

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stearic acid, stearate, sodium stearyl fumarate, glyceryl behenate, kaolin and aerosil.

Afterwards, one or more excipients such as micro-crystalline cellulose or other pharmaceutically acceptable excipients are made into a core (1) in the shape of a pellet (as shown in FIG. 1) by a wet-granulation method. The apparatus for making the core (1) is, for example, a fluidized bed. In step (a), the pellet shaped-core preferably has a size of from 3 mm to 5 mm. In the case of a tablet or a mini-tablet, the core (1) can be formed by the direct tableting method such as by a tablet making machine; and the tablet or mini-tablet made thereby also preferably has a size of from 3 mm to 5 mm.

Preferably, the core (1) used in the present invention is made from at least one of the excipients without any pharmaceutical activity. The excipient useful for the core (1) can be one of the members selected from the group consisting of lactose, starches, mannitol, sodium carboxymethyl cellulose, sodium starch glycolate, sodium chloride, potassium chloride, pigments, salts of alginic acid, talc, titanium dioxide, stearic acid, stearate, micro-crystalline cellulose, glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate, dibasic calcium phosphate, tribasic sodium phosphate, calcium sulfate, cyclodextrin and castor oil.

Afterwards, the above-mentioned solution or suspension is spread onto the core (1). After drying it, layer (2) containing an active ingredient is formed over the core (1). The spreading of the solution or the suspension is completed by, for example, an atomizer.

In addition, the core (1) can be directly produced by a supplier. Readily available cores comprise: (a1) a granule core of sucrose; (a2) a granule core of sucrose and starch; and (a3) a granule core of micro-crystalline cellulose. In this case, step (a) may be adjusted to be supplying a core (1) and then spreading the active ingredient containing solution or suspension on the core (1).

Optionally, one or more adhesives can be added to prepare the core, which are selected from the group consisting of polyvinyl pyrrolidone (PVP), gelatin, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), vinyl acetate (VA), polyvinyl alcohol (PVA), methyl cellulose (MC), ethyl cellulose (EC), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalates (CAP), xanthan gum, alginic acid, salts of alginic acid, Eudragit®, copolymer of methyl acrylic acid/methyl methacrylate with polyvinyl acetate phthalate (PVAP).

Optionally, one or more plasticizers can be further added to prepare the core. Suitable plasticizers are selected from the group consisting of glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.

Optionally, one or more diluents can further be added to prepare the core. Suitable diluents are selected from the group consisting of lactose, starch, mannitol, sodium carboxymethyl cellulose, sodium starch glycolate, sodium chloride, potassium chloride, pigments, salts of alginic acid, talc, titanium dioxide, stearic acid, stearate, micro-crystalline cellulose, glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate, dibasic calcium phosphate, tribasic sodium phosphate, calcium sulfate, cyclodextrin and castor oil.

After step (a), the layer (2) containing the active ingredient can contains 0.25 to 15% (w/w) of stabilizers, 0.5% to 30% (w/w) of anti-tackiness, 0 to 25% (w/w) of plasticizers, 0 to 50% (w/w) of adhesives and the balance of acid-sensitive drugs or pharmaceutically acceptable salts thereof.

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In step (b), the sub-coating layer (3) is coated on the active ingredient layer (2) by spreading the solution or suspension comprising adhesives, plasticizers, anti-tackiness and solvents onto the active ingredient layer (2) containing the core (1) prepared in step (a) and then drying it. The solution or the suspension is spread by being atomized by a nozzle. The nozzle used in the present invention is also well-known to those skilled in the art, thus it is not discussed in detail.

Optionally, plasticizers or other diluents can be added in the solution or suspension prepared by step (b).

The adhesives suitably used in step (b) can be the same one as used in step (a) and also can be a member of the group consisting of polyvinyl pyrrolidone (PVP), gelatin, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), vinyl acetate (VA), polyvinyl alcohol (PVA), methyl cellulose (MC), ethyl cellulose (EC), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate acid (CAP) xanthan gum, alginic acid, salts of alginic acid, Eudragit, and a copolymer of methyl acrylic acid/methyl methacrylate with polyvinyl acetate phthalate (PVAP).

The plasticizer useful in step (b) is selected from the group consisting of glycerin, polyvinyl alcohol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.

The anti-tackiness useful in step (b) is selected from the group consisting of talc, stearic acid, stearate, sodium stearyl fumarate, glyceryl behenate, kaolin, and aerosil.

The solvents useful in step (b) can be the same as those used in step (a) and can be selected from the group consisting of water, alcohols, acetone, isopropanol, dichloromethane and compositions thereof.

The diluents useful in step (b) can be the same as those used in step (a) and can be selected from the group consisting of lactose, starch, mannitol, sodium carboxymethyl cellulose, sodium starch glycolate, sodium chloride, potassium chloride, pigments, salts of alginic acid, talc, titanium dioxide, stearic acid, stearate, micro-crystalline cellulose, glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate, dibasic calcium phosphate, tribasic sodium phosphate, calcium sulfate, cyclodextrin and castor oil.

In step (c), the suspension containing enteric-soluble coating material and solvents is also spread onto the sub-coating layer (3) by atomization by using a nozzle. After drying it, an enteric coating layer (4) is formed over the sub-coating layer (3).

The enteric-soluble coating material suitable for the present invention is selected from the group consisting of hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose of acetate phthalate(CAP), polyvinyl phthalic acetate (PVPA), Eudragit and shellac.

Optionally, plasticizers and anti-tackiness can further be added to the enteric coating layer. The solvents, plasticizers and anti-tackiness useful in step (c) and be the same as those used in step (a).

The plasticizer useful in step (c) is selected from the group consisting of glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.

The anti-adhesive useful in step (c) is selected from the group consisting of talc, stearic acid, stearate, sodium stearyl fumarate, glyceryl behenate, kaolin and aerosil.

The solvents useful in step (c) can be the same as those used in step (a) and can be selected from the group consisting of water, alcohols, acetone, isopropanol, dichloromethane and compositions thereof.

EXAMPLES

Following examples are provided to further explain the present invention. However, the scope of the present invention should not be limited by these examples.

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Example 1

Formulation:		
(1)	core	450 g
(2)	layer containing the active ingredient:	
	omeprazole	80 g
	HPC	16 g
	Polyethylene glycol (PEG 6000)	10 g
	Dibasic sodium phosphate (Na ₂ HPO ₄)	1.4 g
	Tribasic sodium phosphate (Na ₃ PO ₄)	1.4 g
	Talc	24 g
	Pure water	800 ml
(3)	sub-coating layer:	
	HPC	32 g
	PEG 6000	16 g
	Talc	32 g
	Pure water	600 ml
(4)	enteric coating layer:	
	HPMCAS	110.4 g
	Triethyl citrate	30.8 g
	Talc	34.8 g
	Pure water	1,100 ml

Procedure:
10 g of PEG 6000, 16 g of HPC and 800 ml of pure water were mixed together to prepare an aqueous solution.

Then, 1.4 g of dibasic sodium phosphate and 1.4 g of tribasic sodium phosphate were poured and mixed into the prepared aqueous solution.

Subsequently, 80 g of omeprazole and 24 g of talc were poured into the prepared solution to make a suspension containing an active ingredient. The suspension containing the active ingredient was spread, in an atomized manner, onto the cores in a fluidized bed to make an active ingredient layer containing the pellets after drying.

Afterward, a suspension was prepared by mixing 32 g of HPC, 16 g of polyethylene glycol(PEG), 32 g of talc and 600 ml of pure water. The prepared suspension was then spread on the active ingredient layer containing the pellets in atomized manner to make a sub-coating layer over the active ingredient layer after drying.

Finally, a suspension was prepared by mixing 110.4 g of HPMCAS, 30.8 g of triethyl citrate, 34.8 g of talc and 1,100 ml of pure water and then the prepared suspension was spread on the pellets over the sub-coating layer to serve as the enteric coating layer after drying.

Example 2

Formulation:		
(1)	core:	450 g
(2)	active ingredient layer:	
	omeprazole	80 g
	HPMC	12 g
	Polyethylene glycol (PEG 4000)	8 g
	Na ₂ HPO ₄	7.5 g
	Talc	24 g
	Pure water	800 ml
(3)	sub-coating layer	
	HPMC	32 g
	PEG 4000	16 g
	Na ₃ PO ₄	2.4 g

-continued		
Formulation:		
(4)	Talc	32 g
	Pure water	600 ml
	<u>enteric coating layer:</u>	
	HPMCAS	110.4 g
	Triethyl citrate	30g
	Talc	35g
	Pure water	1,100 ml

Procedure:
8 g of Polyethylene glycol, 12 g of HPMC and 800 ml of pure water were mixed together to prepare an aqueous solution.
Then, 7.5 g of dibasic sodium phosphate was added to the prepared solution.
Subsequently, 80 g of omeprazole and 24 g of talc were added to the prepared solution to prepare a suspension. The suspension composition was then spread on the cores in a fluidized bed to prepare an active ingredient layer containing the pellets after drying.
Afterward, 32 g of HPMC, 16 g of polyethylene glycol, 2.4 g of tribasic sodium phosphate, 32 g of talc and 600 ml of pure water were mixed to prepare a suspension composition. The suspension composition was then spread on the active ingredient layer containing the pellets and dried to form sub-coating layers over the active ingredient layers.
Finally, 110.4 g of HPMCAS, 30 g of triethyl citrate, 35 g of talc and 1,100 ml of pure water were mixed together to prepare a suspension composition. The composition was spread on the pellets over the sub-coating layers and was dried to become the enteric coating layer.

Example 3

(1)	core:	420 g
(2)	<u>active ingredient layer:</u>	
	omeprazole	60 g
	polyvinyl pyrrolidone (PVP k30)	12 g
	polyethylene glycol (PEG6000)	8 g
	Na ₃ PO ₄	6.5 g
	Talc	24 g
	Pure water	600 ml
(3)	<u>sub-coating layer:</u>	
	HPMC	24 g
	PEG 6000	12 g
	Na ₃ PO ₄	2.4 g
	Talc	24 g
	Pure water	450 ml
(4)	<u>enteric coating layer:</u>	
	HPMCAS	90 g
	Triethyl citrate	20 g
	Talc	28 g
	Pure water	900 ml

Procedure:
8 g of polyethylene glycol, 12 g of PVP k30 and 600 ml of pure water were mixed to prepare an aqueous solution.
Then 6.5 g of tribasic sodium phosphate was poured in the prepared solution.
Subsequently, 60 g of omeprazole and 24 g of talc were poured into the prepared solution to prepare a suspension containing an active ingredient. Then, the suspension was spread on the cores in a fluidized bed and was dried to make an active ingredient layer containing the cores.

Afterward, a solution of 24 g of HPMC, 12 g of polyethylene glycol, 2.4 g of tribasic sodium phosphate, 24 g of talc and 450 ml of pure water were spread on the active ingredient layer containing the cores and was dried to form the sub-coating layer over the active ingredient layer.
Finally, 90 g of HPMCAS, 20 g of triethyl citrate, 28 g of talc and 900 ml of pure water were mixed together to prepare a suspension composition, and then the suspension composition was spread onto the sub-coating layer of each core and dried to form an enteric coating layer on each core.

Example 4

The pellets prepared according to Example. 1 were filled in capsules made of gelatin.

Example 5

The pellets prepared according to Example. 2 were filled in capsules made of gelatin.

Example 6

(control)
Market-available omeprazole oral formulation.
Dissolution test:
Pellets acquired according to Example. 4, 5 and 6 were tested. The releasing test was carried out according to "Releasing Test, The United States Pharmacopoeia, version 24" in terms of the pH-change.
750 ml of 0.1N aqueous solution of hydrochloride was poured into a tank and then heated to a temperature of 37±0.5° C. The rotation velocity of the paddle was adjusted to be 50 rpm. After two hours, 250 ml of 0.2N aqueous solution of tribasic sodium phosphate was added to the tank. The releasing rate was measured and the graph of the releasing ratio VS time was acquired. The results are listed in table 1 and presented graphically in FIG. 2.
Table 1 (the releasing ratio (%) of the tested pellets in pH-change releasing solution)

		Example. 4		Example. 5		Example. 6	
Time	Ave.					(control)	
		(min)	(%)	St. Error	(%)	St. Error	Ave. (%)
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
20	0.04	0.10	0.40	0.04	1.14	0.22	
60	0.50	0.20	0.14	0.05	1.39	0.29	
80	0.45	0.21	0.83	0.22	1.46	0.33	
120	0.89	0.21	3.39	0.62	1.54	0.41	
150	4.50	0.54	31.10	3.01	22.30	13.94	
180	39.50	2.10	41.20	3.09	40.56	17.77	
210	49.40	2.15	52.23	3.05	50.19	14.38	
240	52.60	3.21	55.25	3.15	54.22	11.75	
270	54.36	2.41	57.52	3.15	56.22	9.33	
300	56.54	2.15	58.21	1.59	57.67	7.58	
330	57.21	2.20	59.21	2.15	58.61	6.79	
360	58.41	0.54	60.25	2.20	58.94	6.65	

From table 1, it was determined that the average dissolution rate in each of Example. 4, Example. 5 and Example. 6 was lower than 10%, which meets the requirements that the enteric coating layer is not allowed to be released in 0.1N aqueous solution of hydrochloride. However, the standard error in each of Example. 4 and Example. 5 is much less than that of Example. 6 that is interpreted to mean that the consistency in the dissolution rate of each of Example. 4 and Example. 5 is superior to that of Example. 6.

Formulation:		
(1)	core:	
	starch	180 g
	micro-crystalline cellulose	220 g
	CaHPO ₄	60 g
	Magnesium stearate	5 g
(2)	active ingredient layer:	
	omeprazole	60 g
	polyvinyl pyrrolidone (PVP k30)	12 g
	polyethylene glycol (PEG 6000)	8 g
	tribasic sodium phosphate	6.5 g
	talc	24 g
	pure water	600 ml
(3)	sub-coating layer	
	HPMC	100 g
	Polyethylene glycol	12 g
	Na ₃ PO ₄	2.4 g
	Talc	24 g
	Pure water	450 ml
(4)	enteric coating layer:	
	copolymer of methacrylic acid/ methacrylate (Eudragit L30D)	24 g
	triethyl citrate	20 g
	talc	48 g
	pure water	500 ml

Procedure:

180 g of starch, 220 g of micro-crystalline cellulose, 60 g of CaHPO₄ and 5 g of magnesium stearate were evenly mixed together and then the mixture was pressed by a tablet-making machine into minitables having a diameter of 3 mm to serve as cores.

8 g of polyethylene glycol, 12 g of polyvinyl pyrrolidone and 600 ml of pure water were mixed to prepare an aqueous solution. Then, 6.5 g of Na₃PO₄ was poured into the prepared aqueous solution.

Subsequently, 60 g of omeprazole and 24 g of talc were added to the prepared solution to prepare a suspension containing an active ingredient. The suspension containing the active ingredient was then spread onto the cores in a fluidized bed and was then dried to prepare the pellets containing the active ingredient.

Afterward, 24 g of HPMC, 12 g of polyethylene glycol, 2.4 g of Na₃PO₄ 24 g of talc and 450 ml of pure water were mixed to prepare a suspension composition, and the composition was spread on the pellets containing the active ingredient to serve as a sub-coating layer after drying.

Finally, 100 g of copolymer of methacrylic acid/methacrylate, 20 g of triethyl citrate, 48 g of talc and 500 ml of pure water were mixed to prepare a suspension composition, and the suspension composition was spread on the sub-coating layer of each core to serve as an enteric coating layer after drying.

Example 8

Formulation:		
(1)	core:	
	anhydrous lactose	90 g
	starch	220 g
	micro-crystalline cellulose	180 g

-continued

Formulation:		
5	CaHPO ₄	50 g
	pure water	100 ml
	magnesium stearate	5 g
(2)	active ingredient layer:	
	omeprazole	80 g
	polyvinyl pyrrolidone (PVP K30)	12 g
	polyethylene glycol (PEG 6000)	8 g
	Na ₃ PO ₄	4.5 g
	Talc	24 g
	Pure water	600 ml
(3)	sub-coating layer:	
	HPMC	24 g
	Polyethylene glycol (PEG6000)	12 g
	Na ₃ PO ₄	2.4 g
	Talc	24 g
	Pure water	450 ml
(4)	enteric coating layer:	
	copolymer of methacrylic acid/ methacrylate (Eudragit L30D)	100 g
	triethyl citrate	20 g
	talc	48 g
	pure water	500 ml

Procedure:

90 g of anhydro-lactose, 220 g of starch, 180 g of micro-crystalline cellulose and 50 g of CaHPO₄ were added to 100 ml of pure water and evenly mixed with 5 g of magnesium stearate, and then the mixture was made into tablets in a tablet-making machine.

8 g of polyethylene glycol and 12 g of polyvinyl pyrrolidone were added to 600 ml of pure water to prepare an aqueous solution. Then, 4.5 g of Na₃PO₄ was added to the prepared solution.

Subsequently, 80 g of omeprazole and 24 g of talc were added into the prepared solution to prepare a suspension containing an active ingredient, and the suspension was spread on the tablets in a fluidized bed to prepare pellets containing the active ingredient-after drying.

Afterward, 24 g of HPMC, 12 g of polyethylene glycol, 2.4 g of Na₃PO₄, 24 g of talc and 450 ml of pure water were mixed to prepare a suspension composition, and the composition was spread on the pellet cores to form a sub-coating layer after drying.

Finally, 100 g of copolymer of methacrylic acid/methacrylate, 20 g of triethyl citrate, 48 g of talc and 500 ml of pure water were mixed to prepare a suspension composition, and the suspension composition was spread on each core over the sub-coating layer to form an enteric coating layer on each core after drying.

Example 9

Formulation:		
60	(1) core:	450 g
	(2) active ingredient layer:	
	lansoprazole	80 g
	HPMC	12 g
	Polyethylene glycol (PEG 6000)	8 g
	Na ₃ PO ₄	6.5 g
	Talc	24 g
	Pure water	600 ml

-continued		
Formulation:		
(3)	sub-coating layer:	
	HPMC	24 g
	Polyethylene glycol (PEG6000)	12 g
	Na ₃ PO ₄	2.4 g
	Talc	24 g
	Pure water	450 ml
(4)	enteric coating layer:	
	copolymer of methacrylic acid/ methacrylate (Eudragit L30D)	60 g
	triethyl citrate	20 g
	talc	48 g
	pure water	500 ml

Procedure:

8 g of polyethylene glycol, 12 g of HPMC and 600 ml of pure water were mixed to prepare an aqueous solution, and then 6.5 g of tribasic sodium phosphate was added to the prepared solution.

80 g of lansoprazole and 24 g of talc were added to the prepared solution to prepare a suspension containing an active ingredient, and the suspension containing the active ingredient was spread on cores in a fluidized bed to prepare pellets coated with the active ingredient layer after drying.

Subsequently, 24 g of HPMC, 12 g of polyethylene glycol, 2.4 g of Na₃PO₄, 24 g of talc and 450 ml of pure water were mixed to prepare a suspension composition, and the composition was spread on the prepared pellets to form a sub-coating layer over each active ingredient layer after drying.

Finally, 60 g of HPMCAS, 20 g of triethyl citrate, 48 g of talc and 500 ml of pure water were mixed to prepare a suspension, and the suspension was spread on each core over the sub-coating layer to form an enteric coating layer after drying.

Example 10

(1)	core:	
	anhydrous lactose	40 g
	starch	200 g
	micro-crystalline cellulose	120 g
	CaHPO ₄	80 g
	Pure water	100 ml
(2)	active ingredient layer:	
	pentoprazole	60 g
	HPMC	19 g
	Polyethylene glycol (PEG 6000)	9 g
	Na ₃ PO ₄	6.5 g
	Talc	24 g
	Pure water	600 ml
(3)	sub-coating layer:	
	HPMC	24 g
	polyethylene glycol (PEG 6000)	12 g
	Na ₃ PO ₄	2.4 g
	Talc	24 g
	Pure water	450 ml
(4)	enteric coating layer:	
	HPMCAS	60 g
	Triethyl citrate	20 g
	Talc	48 g
	Pure water	500 ml

Procedure:

40 g of anhydro lactose, 200 g of starch, 120 g of micro-crystalline cellulose and 60 g of CaHPO₄ were added to 100 ml of pure water to prepare cores after pelletizing.

9 g of polyethylene glycol, 19 g of HPMC and 600 ml of pure water were mixed to prepare an aqueous solution. Then, 6.5 g of Na₃PO₄ was added to the aqueous solution.

Subsequently, 60 g of pentoprazole and 24 g of talc were added to the prepared solution to prepare a suspension containing an active ingredient, and the suspension was spread on the cores in a fluidized bed to prepare pellets coated with an active ingredient layer after drying.

Afterward, 24 g of HPMC, 12 g of polyethylene glycol, 2.4 g of Na₃PO₄, 24 g of talc and 450 ml of pure water were mixed to prepare a suspension, and the suspension was spread on each core over the active ingredient layer to form a sub-coating layer after drying.

Finally, 60 g of HPMCAS, 20 g of triethyl citrate, 48 g of talc and 500 ml of pure water were mixed to prepare a suspension composition, and the composition was spread on each core over the sub-coating layer to form an enteric coating layer.

Example 11

The procedure of Example. 6 was repeated with the exception that the oral formulations to be tested were the mini-tablets made in Example. 7 and tablets made in Example. 8. The testing results are shown in FIGS. 3 and 4. As shown in FIGS. 3 and 4, both the mini-tablets made in Example. 7 and the tablets made in Example. 8 have a releasing ratio of under 10% at 120 min, which meets the requirements that the enteric products are not allowed to be resolved in 0.1N aqueous solution of hydrochloride.

Although the present invention has been explained relative to its preferred embodiment, it is to be understood that many other possible modifications and variations can be made without departing from the spirit and scope of the invention as hereinafter claimed.

What is claimed is:

1. A method for preparing an oral formulation containing acid-sensitive drugs comprising:

(a) spreading a solution or a suspension consisting essentially of stabilizers, an inorganic solvent and acid-sensitive drugs or its pharmaceutically acceptable salts on a core made from one or more excipients, and then drying the spread core to make a core coated with an active ingredient layer;

(b) spreading a composition solution or suspension consisting essentially of adhesives, plasticizer, anti-tackiness and an inorganic solvent on the active ingredient layer containing the core achieved in (a) and then drying it to form a sub-coating layer over the active ingredient layer; and

(c) spreading a suspension comprising enteric-soluble coating material and an inorganic solvent on the sub-coating layer achieved in (b) and then drying it to make an enteric coating layer over the sub-coating layer.

2. The method as claimed in claim 1, wherein the acid-sensitive drugs is substituted benzimidazole gastric anti-secretary agent selected from the group consisting of omeprazole, lansoprazole, pentoprazole and pharmaceutically acceptable salts thereof.

3. The method as claimed in claim 1, wherein the core in step (a) is a pellet core made by a wet granulation method.

4. The method as claimed in claim 1, wherein the core in step (a) is a tablet made by a wet granulation method.

5. The method as claimed in claim 1, wherein the core in step (a) is a mini-tablet made by a wet granulation method.
6. The method as claimed in claim 1, wherein the core (1) is a pellet core.
7. The method as claimed in claim 1, wherein the core (1) is a tablet core made by tablet-making machine.
8. The method as claimed in claim 1, wherein the core (1) is a mini-tablet core made by tablet-making machine.
9. The method as claimed in claim 8, wherein the mini-tablet has a size of from 3 mm to 5 mm.
10. The method as claimed in claim 1, wherein one or more additives selected from the group consisting of adhesives, plasticizers and diluents are further added in step (a) to prepare the core.
11. The method as claimed in claim 1, wherein one or more additives selected from the group consisting of plasticizers and diluents are further added in the solvents of step (b).
12. The method as claimed in claim 1, wherein one or more additives selected from the group consisting of plasticizers and anti-tackiness are further added to the solvents of step (c).
13. The method as claimed in claim 1, wherein the inorganic solvent is water.
14. The method as claimed in claim 1, wherein the adhesives are selected from the group consisting of polyvinyl pyrrolidone (PVP), gelatin, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), vinyl acetate (VA), polyvinyl alcohol (PVA), methyl cellulose (MC), ethyl cellulose (EC), hydroxypropyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), copolymer of methyl acrylic acid/methyl methacrylate with polyvinyl acetate phthalate (PVAP).
15. The method as claimed in claim 10, wherein the plasticizers are selected from the group consisting of glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.
16. The method as claimed in claim 11, wherein the plasticizers are selected from the group consisting of glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.
17. The method as claimed in claim 12, wherein the plasticizers are selected from the group consisting of glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate and castor oil.
18. The method as claimed in claim 10, wherein the one or more diluents are selected from the group consisting of lactose, starch, mannitol, glycolate sodium carboxymethyl cellulose, sodium starch, sodium chloride, potassium chloride, pigments, salts of alginic acid, talc, titanium dioxide, stearic acid, stearate, micro-crystalline cellulose, glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate, dibasic calcium phosphate, tribasic sodium phosphate, calcium sulfate, cyclodextrin and castor oil.
19. The method as claimed in claim 11, wherein the one or more diluents are selected from the group consisting of lactose, starch, mannitol, sodium carboxymethyl cellulose,

- sodium starch, glycolate, sodium chloride, potassium chloride, pigments, salts of alginic acid, talc, titanium dioxide, stearic acid, stearate, micro-crystalline cellulose, glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate, dibasic calcium phosphate, tribasic sodium phosphate, calcium sulfate, cyclodextrin and castor oil.
20. The method as claimed in claim 1, wherein the anti-tackiness are selected from the group consisting of talc, stearic acid, stearate, sodium stearyl fumarate, glyceryl behenate, kaolin and aerosil.
21. The method as claimed in claim 1, wherein the excipient is selected from the group consisting of lactose, starches, mannitol, sodium carboxymethyl cellulose, sodium starch, sodium chloride, potassium chloride, pigments, salts of alginic acid, talc, titanium dioxide, stearic acid, stearate, micro-crystalline cellulose, glycerin, polyethylene glycol, triethyl citrate, tributyl citrate, propanyl triacetate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, cyclodextrin and castor oil.
22. The method as claimed in claim 1, wherein the stabilizers are selected from the group consisting of hydroxides of alkali-metals and alkaline earth metals, bases of phosphates and organic acid salts, and organic amines.
23. The method as claimed in claim 1, wherein the active ingredient layer contains 0.25 to 15% (w/w) of stabilizers, 0.5% to 30% (w/w) of anti-tackiness, 0 to 25% (w/w) of plasticizers, 0 to 50% (w/w) of adhesives and the balance of omeprazole or pharmaceutically acceptable salts thereof.
24. The method as claimed in claim 1, wherein the oral formulation containing acid-sensitive drugs can be filled into a capsule alone to make a pharmacy containing dose-amount of the active ingredients.
25. The method as claimed in claim 1, wherein the oral formulation containing acid-sensitive drugs can be further mixed with other pharmaceutically acceptable excipients and tableted into tablets.
26. The method as claimed in claim 3, wherein the pellets can further be compressed into a tablet.
27. The method as claimed in claim 3, wherein the pellets can further be compressed into a mini-tablet.
28. An oral formulation containing acid-sensitive drugs, comprising:
a core (1) made of one or more excipients,
at least one active ingredient-containing layer (2) having an evenly distributed active ingredient consisting essentially of a stabilizer component, an inorganic solvent component, and an acid-sensitive drug component or its pharmaceutically acceptable salt, the active ingredient-containing layer (2) covering the core (1),
at least one sub-coating layer (3) covering the layer (2) containing the active ingredient, the sub-coating layer (3) consisting essentially of adhesive, plasticizer and tackiness, and inorganic solvent components; and
an enteric coating layer and an inorganic solvent (4) formed over the sub coating layer (3).

* * * * *

DELEGATURA PARA LA PROPIEDAD INDUSTRIAL
FORMULARIO PARA OTORGAR PODER A ABOGADO
EN LOS TRÁMITES DE PROPIEDAD INDUSTRIAL

1. Datos del otorgante

☐ Persona Natural

☒ Persona Jurídica

C.I FARMACAPSULAS S.A.

Nombre o denominación /Razón Social completa (En caso de que haya más de un solicitante, relaciónese en hoja adjunta)

GLORIA EUGENIA HENAO JINETE

Nombre del representante

Tipo de empresa ☐ Micro ☐ Pequeña ☐ Mediana ☒ Otra

Documento de identificación: ☐ C.C. ☐ C.E. ☒ NIT ☐ Otro Número 890.105.927-3

Nacionalidad/País de constitución	Dirección del otorgante	
Colombiana	Calle 79 B No.78 C - 21 Barranquilla	
Dirección electrónica	No. Fax	Número telefónico

2. Datos del apoderado:

REYES VILLAMIZAR JOSE LUIS

79.152.473

44655

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Nacionalidad/País de constitución	Dirección del otorgante	
Colombiana	Cra. 17 No. 88 -23 Of. 205	
Dirección electrónica	No. Fax	Número telefónico
info@reyes-abogados .com	6212542	655 77 95 / 621 26 31

☐ Autorizo expresamente a la Superintendencia de Industria y comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico.

Mediante el presente documento, la persona indicada en el punto 1 de este documento nombra a la persona que se identifica en el punto 2 como apoderado para las actuaciones que se relacionan a continuación:

3. Actuaciones en cuestión:

Este poder concierne:

☒ Exclusivamente, para adelantar trámites de oposición contra solicitudes de patente de invención.

☐ Incluyendo, sin limitarse, a la oposición contra la solicitud de patente tramitada en el Exp.13-111735

NOMBRE	NÚMERO DE SOLICITUD O REGISTRO

NOTA: Si el espacio anterior no es suficiente, por favor relacione las actuaciones en hoja anexa.

4. Alcance del poder:

☒ Confiero expresamente al apoderado todas las facultades legales para que represente mi(s) interés(es) en la(s) actuación(es) señalada(s) en el punto 3 de este documento, incluyendo:

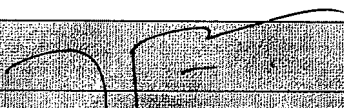
☒ Desistir de la(s) solicitud(es) y de las demás actuaciones

☐ Renunciar a los derechos del registro de signos distintivos o de nuevas creaciones

☐ Transigir

☐ Recibir

☐ Conciliar

5. Firma	
	
Nombre del Firmante	Firma
GLORIA EUGENIA HENAO JINETE	JOSE LUIS REYES VILLAMIZAR
C.C. 22.406.423 de Barranquilla	Tarjeta Profesional 44655

- / -

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*** Conceptos Pagados ***				
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	103.000.00	103.000.00
		1608 N.CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL		\$103.000.00
				=====

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

Responsable: _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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