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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **EXPEDIENTE 13-111-735**

TÍTULO SOLICITADO: **"COMPOSICIÓN PARA CÁPSULAS DURAS ENTÉRICAS Y CÁPSULA SURA ENTÉRICA PREPARADA USANDO LA COMPOSICIÓN"**

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

PRIORIDAD: **KO 10-2010-0103053 21/10/2010**

SOLICITANTE: **SAMSUNG FINE CHEMICALS CO., LTD.**

APODERADO: **JUAN PABLO CADENA SARMIENTO**

TRÁMITE: **SUSTENTACIÓN 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 **FARMACÁPSULAS S.A.,** en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. RATIFICACIÓN

Mediante el presente escrito, ratifico que la solicitud **13-111-735**, referida a una composición para cápsulas duras entéricas y las cápsulas obtenidas mediante dicha composición, no cumple con los requisitos de patentabilidad y no puede, por ello, ser objeto de privilegio de patente.

En efecto, en la oposición presentada el 25 de septiembre de 2013, se demostró que la solicitud en trámite no cumple con los requisitos para ser concedida, debido a que carece de claridad, concisión y soporte en la descripción.

Se mencionó que el documento US 6346269 (D1) publicado por Fang-Hsiung Hsiao, titulado "Method for preparing an oral formulation containing acid-sensitive drugs and oral formulation made thereby" del 12 de febrero de 2002, revela las característica técnicas esenciales de la solicitud al describir una formulación oral que comprende ftalato de hidroxipropil metil celulosa (HPMCP), hidroxiproil metil celulosa (HPMC), al menos un agente alcalino y estabilizadores, así como los polioles que son descritos.

Por lo tanto, 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.

Por último, teniendo en cuenta el efecto ventajoso de la solicitud 13-111-735, se mencionó que éste había sido logrado por la anterioridad en mención al reducir la actividad de la cápsula con el principio activo.

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 novedad y altura inventiva.

II. COMPLEMENTO DE INFORMACIÓN

De la lectura de la descripción de la solicitud 13-111-735, se observa que el problema técnico objetivo puede ser planteado como la necesidad de obtener cápsulas de HPMCP con una estabilidad y resistencia mecánica aumentadas (páginas 4 y 5):

> Las cápsulas de gelatina tienen una alta productividad industrial y una elevada competitividad de precios. No obstante, si las cápsulas de gelatina contienen 10 % en peso de humedad o menos, pueden perder plasticidad y pueden exhibir un deterioro serio en la resistencia al impacto. Las preocupaciones sobre la enfermedad de la encefalopatía espongiforme bovina ha limitado el uso de las cápsulas de gelatina. Por estas razones, las cápsulas de HPMC a base de plantas, preparadas sin gelatina, y las cápsulas de HPMCP entéricas han atraído la atención.
>
> Sin embargo, las cápsulas de HPMCP convencionales tienen baja transparencia y son frágiles con un contenido bajo de humedad de 10 % en peso o menos, por ejemplo. Adicionalmente, cuando se almacenan bajo condiciones severas de temperatura elevada, las cápsulas de HPMCP pueden perder lentamente
>
> humedad interior y endurecerse, porque incluyen un exceso de un agente neutralizante (v.g., un agente alcalino). Por lo demás, el agente neutralizante puede separarse de las cápsulas endurecidas, lo cual se denomina también separación de sal, en un período relativamente corto de tiempo, la mayoría de las veces en 30 días.

Para lograr dicho efecto, el solicitante refiere la siguiente composición de la reivindicación 1:

> [Reivindicación 1]
> Una composición para 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 a alrededor de 50 partes en peso de hidroxipropilmetilcelulosa (HPMC);
> alrededor de 5,5 a alrededor de 8,5 partes en peso de un agente alcalino; y
> alrededor de 2 partes a alrededor de 15 partes en peso de un poliol, el cual tiene por lo menos tres grupos hidroxilo,
> en donde las cantidades del HPMCP, la HPMC, el agente alcalino y el poliol en partes en peso se basan en 100 partes en peso del peso total del HPMCP y la HPMC.

Frente a lo anterior, deseamos poner de presente que el ingrediente principal empleado en esta composición es el HPMCP, el cual es ampliamente conocido como un material de recubrimiento entérico (Brochure Shin-Etsu Chemical Co., Ltd, Septiembre 2002):

> Although HPMCP was developed and used originally as an enteric coating agent, its favourable properties have led to extension of its range of applications into other fields, including sustained-release preparations, binders and microcapsule bases. In the above-mentioned applications, HPMCP is usually used alone, but can be used in combination with other polymers, as in the case of the sustained-release preparations.
> The descriptions of HPMCP given here apply mainly to coating applications.

Incluso, el uso de HMPCP para obtener una cubierta entérica ya había sido divulgado en la anterioridad US 6346269 (D1), mencionada en el escrito de oposición del 25 de septiembre de 2013, (*Method for preparing an oral formulation containing acid-sensitive drugs and oral formulation made thereby"* del 12 de febrero de 2002) (col. 13, ln 25 a 35):

> **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).

Este documento también revela los mismos componentes mencionados por la materia reclamada por la solicitud en mención (col. 4 y 14) como el HPMCP, HPMC, hidróxido, glicerina, manitol y propilenglicol:

> 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.

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 stablizers 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.

De acuerdo con lo anterior, se ha demostrado que en el estado del arte ya se conocían cápsulas a base de HPMCP, que contenían HPMC, agentes alcalinos y polioles, por lo tanto, no se puede considerar que la materia reclamada por la reivindicación 1 sea nueva o inventiva, pues los componentes de la misma ya habían sido divulgados en el arte.

Por otro lado, el documento US5385739 (D2), titulado "*Stable compositions of gastroprotected omerprazole microgranules and process for the production thereof*", publicado el 31 de enero de 1995, se refiere al uso de HPMCP junto con HPMC para lograr cubiertas entéricas con óptima estabilidad (p. 2, col. 2, ln. 50 a 65):

mm).

To ensure good stability of the active principle during storage of the microgranules according to the invention, the moisture level of the active layer is less than 1%, preferably less than 0.5%.

Additionally, the microgranule according to the invention advantageously comprises an additional protective layer of the active layer consisting of mannitol and of a binding agent, in order to definitively isolate the core, on which the omeprazole is applied, from the external coating layer intended to provide gastroprotection of the active cores.

Preferentially, the binding agent is hydroxypropyl methylcellulose (HPMC) whereas the gastroresistant layer comprises hydroxypropyl methylcellulose phthalate (HPMCP) or anionic copolymers of methacrylic acid and talc.

In order to satisfy the in vitro dissolution criteria of the omeprazole microgranules, according to which at

Así mismo, el documento US5540945 (D3), titulado "*Pharmaceutical preparations for oral administration that are adapted to release the drug ar appropiate sites in the intestines*", publicado julio 30 de 1996, se refiere a cápsulas a base de HPMCP y HPMC (p.3, p. 8, col. 3, ln. 24 a 50):

Fig. 3C

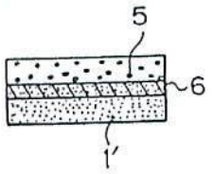


Fig. 3E

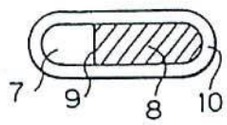
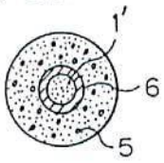


Fig. 3D



The first layer comprises an enteric or water-soluble ingredient. The first layer is present in order to insulate the core from the second layer, thereby controlling the time at which the active ingredient starts to be released. Specific examples of the component of the first layer include: enteric ingredients such as hydroxypropylmethyl cellulose phthalate (HPMCP), hydroxypropylmethyl cellulose acetate succinate (HPMCAS), methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methyl methacrylate-chlorotrimethylammonium ethyl methacrylate copolymer, cellulose acetate phthalate (CAP), cellulose propionate phthalate, cellulose acetate maleate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, styrene-acrylic acid copolymer, and methyl acrylate-methacrylic acid copolymer; and water-soluble ingredients such as cellulosic derivatives (e.g. acetyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and carboxymethyl cellulose sodium) and natural high-molecular weight compounds (e.g. gelatin). The release start time can be delayed by adding insoluble ingredients such as ethyl cellulose (E.C). Such insoluble ingredients can be added in amounts ranging from 0 to 50% of the first layer.

Each of the first, second and third layers may have plasticizers, antistats and other compounds incorporated therein for the purpose of improving coating and film-forming properties.

Así mismo, el documento US 4138013 (D4), titulado "*Enteric capsules*" del 6 de febrero de 1979, presenta cápsulas entéricas conformadas por HPMC y HPMCP (Col. 1, ln 10 a 20, col. 3, ln. 40 a 55)

SUMMARY AND DETAILED DESCRIPTION:

The present invention relates to enteric capsules. More particularly, the invention relates to pharmaceutical capsules having capsule body and cap portions formed by dipmolding using a homogeneous film-forming mixture comprising (1) gelatin and an ammonium salt of hydroxypropyl methylcellulose phthalate polymer, or (2) hydroxypropyl methylcellulose and an ammonium salt of cellulose acetate phthalate polymer, or (3) gelatin and an ammonium salt of a copolymer of methacrylic acid and methacrylic acid alkyl ester; optionally in combination with other ingredients; and to methods for the production of such pharmaceutical capsules.

sules.

The enteric capsules of the present invention, which advantageously meet these objects, have capsule body and cap portions formed by dip-molding using a homogeneous film-forming mixture comprising (1) gelatin and an ammonium salt of hydroxylpropyl methylcellulose phthalate polymer, or (2) hydroxypropyl methylcellulose and an ammonium salt of cellulose acetate phthalate polymer, or (3) gelatin and an ammonium salt of a copolymer of methacrylic acid and methacrylic acid alkyl ester optionally in combination with additional ingredients such as plasticizer and/or coloring agent.

In manufacturing enteric capsules in a series of steps

que contienen glicerina y propilenglicol (Col. 4, ln. 37)

as used in the usual hard shell capsules are suitable. Up to 5% (by weight of the dry gelatin or HPMC) of a plasticizer, such as glycerine or propylene glycol, may be added if desired.

que presentan una excelente resistencia mecánica y estabilidad (col. 3, ln- 51 a 56, col. 6, ln. 25 a 34):

features.

The new enteric capsules of the invention have excellent enteric properties and pharmaceutical acceptability. They are chemically and physically stable and do not develop significantly increased acidity during storage and use. In addition, they have a uniform wall thickness and a low percentage of manufacturing defects.

Although it is known in the prior art that the men-

prior art enteric capsules, all pass the described enteric dissolution test. Thus, in the aging test simulating one year aging after manufacture (storage for 4 weeks at 40° C. under 40% relative humidity), the capsules of the present invention did not dissolve in gastric fluid but dissolved promptly in intestinal fluid. Also, these capsules when produced with coloring agents in the dipping solution did not undergo adverse color change under aging conditions. Moreover, the capsules had excellent retention of elasticity, transparency and lustre under aging. Significantly, the capsules were free of any tendency to generate any odor of ammonia under aging.

I claim:

De acuerdo a lo anterior, queda demostrado que a la fecha de prioridad reivindicada por la solicitud 13 111 735 ya varios documentos habían revelado la composición para cápsulas que contienen HPMCP, HPMC, polioles y agentes básicos, así como también rangos de concentración de los mismos similares. Por lo anterior, no se puede considerar que la materia reclamada por la reivindicación 1 sea nueva.

Mas aún, en documentos como la patente US 41380, se divulga la mejora en estabilidad física y química de este tipo de cápsulas, por lo tanto, el efecto reclamado en la presente solicitud no es sorprendente o inesperado para este tipo de composiciones para cápsulas.

Por otra parte, la reivindicación 2 se refiere a las características del HPMCP como se observa a continuación:

> [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.

Frente a la reivindicación 2, deseamos poner de presente que según la monografía de la farmacopea USP 34- NF29 para HPMCP, ésta es definida como un éster de HPMC con porcentajes definidos de grupo metoxi, hidropropoxi y ftalilo, como se lee a continuación:

> *Hypromellose Phthalate is a monophthalic acid ester of hydroxypropyl methylcellulose. It contains methoxy (–OCH_3), hydroxypropoxy (–$OCH_2CHOHCH_3$), and phthalyl (o-carboxybenzoyl, $C_8H_5O_3$) groups. It contains not less than 21.0 percent and not more than 35.0 percent of phthalyl groups, calculated on the anhydrous basis.* (USP34–NF29 Page 1550, Pharmacopeial Forum: Volume No. 30(3) Page 984 – 2011.)

Adicionalmente, de la lectura de un brochure disponible en el mercado, se sabe que estos son parámetros comúnmente empleados a nivel industrial para referirse a diferentes grados de HPMCP y que tales rangos reclamados en la reivindicación 2 realmente equivalen a rangos ya conocidos e incluso determinados por el grado de HPMCP referidos como HP-55, HP-55S, y HP-50 en el siguiente fragmento del brochure (Brochure Shin-Etsu Chemical Co., Ltd, Septiembre 2002):

The specifications for HPMCP are listed in Table 4 . HPMCP meets all the requirements of US/NF Hydroxypropyl Methylcellulose Phthalate, EP Hypromellose Phthalate or JP Hydroxypropyl Methyl-cellulose Phthalate.

Shin-Etsu Chemical performs strict quality control to meet GMP guidelines.

Table 4: Specifications of HPMCP

Item/Grade	HP-55	HP-55S	HP-50
Labelled viscosity (cst)	40	170	55
Description and solubility	conforms		
Identification (Infrared Absorption)	conforms		
Viscosity (cst)	32-48	136-204	44-66
Water	not more than 5.0%		
Residue on ignition	not more than 0.20%		
Chloride	not more than 0.07%		
Heavy Metals	not more than 0.001%		
Free phthalic acid	not more than 1.0%		
Phthalyl content	27.0-35.0%		21.0-27.0%
Methoxy content	18.0-22.0%		20.0-24.0%
Hydroxypropoxyl content	5.0-9.0%		6.0-10.0%

Por lo tanto, la reivindicación 2 pareciera referirse a HPMCP grado HP-50 por los porcentajes allí referidos. Dado que estos son porcentajes estandarizados para cierto tipo de grado, no es posible decir que tienen novedad o nivel inventivo.

De acuerdo a lo anterior, se ha establecido la carencia de novedad y nivel inventivo de la materia reclamada por el solicitante.

III. PRUEBAS

Ruego que se tengan como tales, además de aquellas que el Despacho considere oficiosamente, las siguientes:

1. El documento US 4993137 titulado "*Method of manufacturing hard capsules*" publicada en 19 Febrero de 1991, de Araume et al, portada y página 1.

2. Brochure Shin-Etsu Chemical Co., Ltd, Septiembre 2002, todo el documento

3. El documento US5385739, titulado "*Stable compositions of gastroprotected omerprazole microgranules and process for the production thereof*", publicado el 31 de enero de 1995, p. 2, col. 2, ln. 50 a 65

4. El documento US5540945, titulado "*Pharmaceutical preparations for oral administration that are adapted to release the drug ar appropiate sites in the intestines*", publicado julio 30 de 1996, p.3, p. 8, col. 3, ln. 24 a 50.

5. Monografía Farmacopea USP34–NF29 Page 1550, Pharmacopeial Forum: Volume No. 30(3) Page 984 – 2011

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Remarks:
This application was filed on 06-09-2010 as a divisional application to the application mentioned under INID code 62.

(54) Dosage form containing pantoprazole as active ingredient

(57) Dosage forms for oral administration of the magnesium salt of pantoprazole are described.

EP 2 316 454 A1

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Description

Technical field

[0001] The present invention relates to the field of pharmaceutical technology and describes a dosage form for oral administration of the magnesium salt of pantoprazole. The invention additionally relates to proces-ses for producing the dosage form.

Prior art

[0002] It is generally known to coat peroral administration forms, e.g. tablets or pellets which contain an acid-labile active compound, with an enteric coating which, after passage through the stomach, rapidly dissolves in the alkaline medium of the intestine. Examples of such acid-labile active compounds are acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors), in particular pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726 and EP-A-0 268 956. On account of their H^+/K^+ ATPase-inhibiting action, these are of importance in the therapy of diseases, which are due to increased gastric acid secretion. Examples of active compounds from this group which are commercially available are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-di-methoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl)-1H-benzimidazole (INN: rabeprazole).

[0003] Because of their strong tendency to decompose in a neutral and, in particular, in an acidic environment, where strongly colored decomposition products are also formed, for oral preparations it is also necessary in this case to protect the active compounds from the action of acids. In the case of the strongly acid-labile pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, it is moreover necessary to process these in the tablet core or in pellets in the form of their alkaline salts, for example as sodium salts, or together with alkaline substances. Since the substances suitable for enteric coatings are those having free carboxyl groups, the problem results that the enteric coating is partly dissolved or even dissolved from inside because of the alkaline medium in the interior and the free carboxyl groups promote the decomposition of the active compounds. It may therefore be necessary to provide an isolating intermediate layer (subcoating) between the enteric coating and the alkaline tablet core or pellet. It is proposed in EP-A-0 244 380 to coat cores which contain the active compound together with alkaline compounds or as an alkaline salt with at least one layer of nonacidic, inert pharmaceutically acceptable substances, which are soluble in water or rapidly decompose in water, before the enteric layer is applied. The intermediate layer or intermediate layers act as pH-buffering zones in which the hydrogen ions diffusing in from outside can react with the hydroxyl ions diffusing from the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substances into the intermediate layer(s). In practice, it is possible by this process to obtain somewhat stable preparations. However, relatively thick intermediate layers are needed in order to avoid the unsightly discolorations occurring even in the case of only slight decomposition. Moreover, a considerable effort is to be made in the preparation to avoid traces of moisture.

[0004] In EP-A-0 519 365, a formulation on the principle of the alkaline core coated with a water-soluble intermediate layer and an enteric coating is proposed for the active compound pantoprazole, in which improved stability is achieved by use of polyvinylpyrrolidone and/or hydroxypropylmethylcellulose as binders for the alkaline core. It is disclosed that as binder a polyvinylpyrolindone of higher molecular weight is used.

[0005] EP-A-0 342 522 discloses a formulation for acid-sensitive benzimidazoles in which, between the alkaline core and the enteric coating, an intermediate layer is located which is composed of only slightly water-soluble film-forming material, such as ethylcellulose and polyvinyl acetate, and a slightly water-soluble finely granular inorganic or organic material suspended therein, such as, for example, magnesium oxide, silicon oxide or sucrose fatty acid esters.

[0006] EP-A-0 277 741 describes spherical granules having a core which is coated with spray powder, which contains low-substituted hydroxypropylcellulose and a benzimidazole compound having anti-ulcer activity. These granules can be coated with an enteric coating agent.

[0007] EP-A-1 213 015 discloses an oral pharmaceutical composition with delayed release of proton pump inhibitors.

[0008] As the abovementioned prior art shows, the production of peroral administration forms for acid-labile active compounds requires technically complicated processes.

[0009] The International Patent Application WO97/41114 describes a specific process for the preparation of magnesium salts of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. Inter alia, the preparation of the magnesium salt of pantoprazole is also described by way of example. According to the analysis data indicated, the salt prepared is pantoprazole magnesium in anhydrous form.

[0010] International Patent Application WO00/10995 describes the dihydrate of the magnesium salt of pantoprazole. It is disclosed that the dihydrate of the magnesium salt of pantoprazole has inter alia improved stability properties as in

comparison to pantoprazole itself or to pantoprazole sodium sesquihydrate.

Description of the invention

[0011] It is an object of the present invention to provide a dosage form for oral administration of pantoprazole magnesium salt, which dosage form can be produced without great technical complexity, which takes account of the acid lability of pantoprazole and which makes available the pantoprazole magnesium salt effectively for the body in such a way that an optimal active ingredient profile and thus action profile is achieved.

[0012] Pantoprazole magnesium oral pharmaceutical dosage forms, available as delayed release forms are found in-vitro to have prolonged dissolution times as compared to corresponding dosage forms containing pantoprazole sodium. From a pharmakokinetic point of view it may thus be expected that pantoprazole magnesium oral dosage forms may have clinical disadvantages, e.g. delayed onset of action as compared to pantoprazole sodium oral dosage forms. Surprisingly, it has been found now that pantoprazole magnesium oral dosage forms have unexpected release profiles of active ingredient and clinical advantages.

[0013] In one aspect the invention therefore relates to an oral pharmaceutical dosage form comprising pantoprazole magnesium together with pharmaceutically acceptable excipients.

[0014] Surprisingly it has also been found now that oral dosage forms for pantoprazole magnesium salt comprising low molecular weight polyvinylpyrrolidone as excipient show stability and a distinctly improved release profile for the active ingredient as compared to oral dosage forms for pantoprazole magnesium salt known from the art.

[0015] The invention therefore also relates to a dosage form for oral administration of pantoprazole magnesium salt comprising a therapeutically effective amount of the pantoprazole magnesium salt together with low molecular weight polyvinylpyrrolidone and one or more other suitable pharmaceutical excipients.

[0016] A dosage form means, in particular, a medicinal dosage form such as a tablet, a coated tablet, a multiparticulate form such as pellets or pellets and microtablets in a capsule or a multiple unit tableted dosage form (such as disclosed in WO 96/01623), with the dosage form advantageously being designed so that the pantoprazole magnesium salt is released, or made available effectively for the body, in such a way that an optimal active ingredient profile, and thus action profile, is achieved. Unit in connection with the multiple unit tableted dosage form refers to an individual unit containing the pantoprazole magnesium salt, which individual unit can be a small bead, particle, granule or pellet, in connection with the invention also referred to as pellet. Suitable dosage forms are for example disclosed in EP-A-0 519 365, EP-A-0 244 380, EP-A-1 213 015, EP-A-1 105 105, EP-A-1 037 634, EP-A-1 187 601 and EP-A-1 341 528.

[0017] The oral dosage form of the invention is preferably a dosage form with modified release of the active ingredient, in particular with delayed release of active ingredient. Particularly preferred is an enteric coated dosage form, comprising at least one enteric coating layer which is stable and does not release the active ingredient under acidic conditions but rapidly dissolves in neutral conditions and in particular in the alkaline medium of the intestine. In a further preferred embodiment the dosage form according to the invention in addition to the enteric coating layer contains one or more intermediate layers (subcoating layers). In another embodiment the dosage form according to the invention comprises at least one enteric coating layer but does not contain an intermediate layer.

[0018] Pantoprazole is the INN (International Nonproprietary Name) for the compound 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole. The magnesium salt of pantoprazole is the chemical compound magnesium bis[5-[difluoromethoxy]-2-[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazolide]. In connection with the invention the pantoprazole magnesium salt can also be present in hydrate form (e.g. monohydrate, sesquihadrate or dihydrate). A particular preferred hydrate in connection with the invention is the dihydrate of the magnesium salt of pantoprazole with the chemical name magnesium bis[5-[difluoromethoxy]-2-[[3,4-dimethoxy-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazolide] dihydrate. The synthesis of the magnesium salt of pantoprazole is described for example in International Patent Application WO97/41114 and the synthesis of the dihydrate of the magnesium salt of pantoprazole is disclosed in International Patent Application WO00/10995.

[0019] Because of a great tendency to decompose in a neutral and, in particular, acidic environment, which also results in highly colored decomposition products, for oral compositions, it is preferred on the one hand to keep the magnesium salt of pantoprazole in an alkaline environment and, on the other hand, to protect it from exposure to acids. It is generally known to coat tablets or pellets, which contain an acid-labile active ingredient with an enteric coating which, after passage through the stomach, rapidly dissolves in the alkaline medium in the intestine. In the case of pantoprazole, which is very acid-labile, it is preferred to process it in the tablet core or in pellets in the form of its alkaline salts, and preferably together with alkaline substances. Since the substances suitable for enteric coatings contain free carboxyl groups, a problem arises when the enteric coating is partly or even completely dissolved from the inside because of the alkaline medium in the interior, and the free carboxyl groups promote decomposition of the active ingredients. It is therefore preferred to provide a sealing intermediate layer (subcoating) between the enteric coating and an alkaline tablet or pellet core. EP-A 0244380 proposes to coat cores, which contain the active ingredient together with alkaline compounds or as alkaline salt with at least one layer, which is soluble in water or rapidly disintegrates in water, of nonacidic, inert pharmaceutically-

acceptable substance before the enteric layer is applied.

[0020] The intermediate layer or intermediate layers act as pH-buffering zones in which hydrogen ions, which diffuse in from the outside, are able to react with the hydroxyl ions which diffuse out of the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substance into the intermediate layer (s). It is possible in practice by this method to obtain rather stable compositions.

[0021] The invention therefore also relates to an oral dosage form in pellet or tablet form for magnesium salt of pantoprazole comprising a therapeutically effective amount of the magnesium salt of pantoprazole together with one or more other pharmaceutical excipients in a pellet or tablet core, at least one subcoating (intermediate layer) and an outer enteric layer which is soluble in the small intestine.

[0022] The invention further relates to an oral dosage form in pellet or tablet form for magnesium salt of pantoprazole comprising a therapeutically effective amount of the magnesium salt of pantoprazole together with one or more other pharmaceutical excipients in an alkaline pellet or tablet core, at least one subcoating (intermediate layer) and an outer enteric layer which is soluble in the small intestine.

[0023] In another embodiment the invention also relates to an oral dosage form in pellet or tablet form for magnesium salt of pantoprazole comprising a therapeutically effective amount of the magnesium salt of pantoprazole together with polyvinypyrrolidon and optionally one or more other pharmaceutical excipients in an alkaline pellet or tablet core, at least one subcoating (intermediate layer) and an outer enteric layer which is soluble in the small intestine.

[0024] In another embodiment the invention also relates to an oral dosage form in pellet or tablet form for magnesium salt of pantoprazole comprising a therapeutically effective amount of the magnesium salt of pantoprazole together with PVP90 and optionally one or more other pharmaceutical excipients in an alkaline pellet or tablet core, at least one subcoating (intermediate layer) and an outer enteric layer which is soluble in the small intestine.

[0025] In another embodiment the invention also relates to an oral dosage form in pellet or tablet form for magnesium salt of pantoprazole comprising a therapeutically effective amount of the magnesium salt of pantoprazole together with low molecular weight polyvinypyrrolidon and optionally one or more other pharmaceutical excipients in an alkaline pellet or tablet core, at least one subcoating (intermediate layer) and an outer enteric layer which is soluble in the small intestine.

[0026] In one embodiment of the invention the oral dosage form is a multiple unit tableted dosage form, with individual enteric coating layered units containing pantoprazole magnesium salt and optionally other excipients.

[0027] Further suitable pharmaceutical excipients, which may be used in the dosage form according to the invention are pharmaceutical excipients such as fillers, (additional) binders, disintegrants or else lubricants and release agents. Other suitable excipients, which may be present in the dosage form of the invention are, for example, flavoring substances (such as flavors and sweeteners), buffer substances, preservatives, coloring substances (such as iron oxid yellow or red), wetting agents, surfactants (such as sodium laurylsulfate) or else emulsifiers. Flavors are usually added in a proportion of from 0.05 to 1 % by weight. Other flavoring substances by way of example are acids such as citric acid, sweeteners such as saccharin, aspartame, cyclamate sodium or maltol, which are added according to the desired result.

[0028] Suitable binders which can be used for preparing the tablet or pellet core are polyvinylpyrrolidone (PVP), hydroxypropymethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, gelatine, whereby PVP is preferred.

[0029] In a preferred embodiment the invention also relates to a dosage form for oral administration of pantoprazole magnesium salt comprising a therapeutically effective amount of the pantoprazole magnesium salt together with polyvinylpyrrolidone (PVP) as a binder and one or more other suitable pharmaceutical excipients.

[0030] The polyvinylpyrrolidone (PVP) employed as binder according to the invention can be of molecular weight in the range of 2.000 - 1.500.000. In one embodiment according to the invention PVP 90 (average molecular weight about 1.000.000 - 1.500.000) or PVP in the range of from 600 000 to 700 000 can be mentioned as preferred. In another embodiment of the invention the PVP is a water-soluble PVP with a low average molecular weight and is preferably used as binder in the dosage form. Low average molecular weight in connection with the invention refers to PVP with an average molecular weight below 300 000, preferably below 100 000, particularly preferably below 70 000, more particularly preferably below 60 000, most particularly preferred below 40 000. Examples, which may be mentioned, are Kollidon 12 PF (molecular weight 2 000-3 000), Kollidon 17 PF (molecular weight 7 000-11 000), Kollidon 25 (molecular weight 28 000-34 000) and Kollidon 30 (molecular weight 44 000-54 000), whereby Kollidon 25 is preferred.

[0031] The proportion (in percent by weight based on the finished dosage form) of PVP as a binder (and, where appropriate, additional other binders) may preferably be according to the invention from 0.5 to 15 % by weight. The proportion of PVP is preferably from 1 to 5 % by weight, particularly preferably from 1.5 to 3.5 % by weight.

[0032] Suitable fillers in connection with the invention are mannitol, lactose, starch, cellulose and calcium phosphate, whereby mannitol is preferred. In one embodiment of the invention mannitol is the sole filler used for the oral dosage forms according to the invention.

[0033] For a basic reaction of the pellet or tablet core (= alkaline tablet or pellet core) it is mixed (where required increase in pH is not achieved simply by using an active-ingredient salt) with an inorganic base. Mention may be made in this connection of, for example, the pharmacologically-suitable (tolerable) alkali-metal, alkaline-earth-metal or earth-

metal salts of weak acids and the pharmacologically-suitable hydroxides and oxides of alkaline-earth and earth metals. Sodium carbonate may be mentioned as a base to be emphasized by way of example.

[0034] Besides filler and binder, other ancillary substances, in particular lubricants and nonstick agents, and tablet disintegrants, are used in the manufacture of tablet cores. Examples of lubricants and nonstick agents, which may be mentioned, are higher fatty acids and their alkali-metal and alkaline-earth-metal salts, such as calcium stearate. Suitable disintegrants are, in particular, chemically inert agents. Tablet disintegrants, which may be mentioned as preferred, are crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcelluloses, sodium starch glycolate and pregelatinized starch.

[0035] In one embodiment of the invention the oral dosage form according to the invention is a tablet and comprises as excipients for the tablet core sodium carbonate, mannitol, crospovidone, polyvinylpyrrolidone and calcium stearate.

[0036] In another embodiment of the invention the oral dosage form according to the invention is in pellet form on the basis of nonpareilles/seeds and the pellet core comprises starch as excipient. It has been found surprisingly that by using starch as excipient in the pellet core (based on nonpareilles/seeds) the release of the pantoprazole magnesium from the pellet core is faster and increased as compared to pellets without starch in the pellet core. Suitable types of starch, which can be used in this connection are different types of starch such as corn starch, potatoe starch, rice starch, wheat starch, preferably pregelatinized starch and in particular pregelatinized corn starch (Starch 1500). In a preferred embodiment according to the invention the amount of pregelatinized starch present in the pellet core is in the range of 0.5 - 4% per weight (based on the total weight of the pellet core), particularly preferably in the range of 1 - 3% per weight.

[0037] The pellet core may contain additional excipients such as those mentioned above and those mentioned in connection with tablet cores (e.g. binders, stabilizers, disintegrants, surfactants and wetting agents).
Wetting agents in this connection preferably refers to synthetic tensides (such as polysorbate, spans, brij), sulfate- and sulfonate salts of fatty acids (such as sodium dodecylsulfate), non-ionic tensides (such as poloxamer) and glycerol esters of fatty acids. In a preferred embodiment SDS (sodium dodecylsulfate) is present. Binders, which may be present are for example PVP, HPMC, hydroxypropylcellulose (HPC) and gelatine. Disintegrants, which may be present are crosslinked polyvinylpyrrolidone, crosslinked sodium carboxymethylcelluloses and sodium starch glycolate.

[0038] In another embodiment of the invention the oral dosage form according to the invention comprises as excipients sodium carbonate, sodium laurylsulfate, pregelatinized starch, polyvinylpyrrolidone and sucrose [Pellets]. The oral dosage form is preferably a pellet on the basis of nonpareilles.

[0039] In respect of the intermediate layer(s) to be applied to a pellet core or tablet core, reference may be made in particular to those water-soluble layers such as are usually used before application of layers which are resistant to gastric juice, or such as are described e.g. in DE-OS 39 01 151. Examples, which may be mentioned of film polymers, which can be used for the intermediate layer are hydroxypropylmethylcellulose and/or polyvinylpyrrolidone, to which plasticizers (such as, for example, propylene glycol) and/or other additives (e.g. talc as an anti-sticking agent) and auxiliaries (e.g. buffers, bases or pigments) can also be added if desired.

[0040] In one embodiment of the invention the oral dosage form according to the invention comprises intermediate layer(s) based on hydroxypropylmethylcellulose as film polymer.

[0041] The expert knows, on the basis of his technical knowledge, what outer layers, which are resistant to gastric juice can be used. Examples of suitable polymers for the enteric coating are methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl -acrylate copolymer (Eudragit® L, S, or Eudragit® L30D) or cellulose derivatives, such as carboxymethylethylcellulose (CMEC, Duodcel®), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HP50, HPSS), hydroxypropylmethylcellulose acetate succinate (HPMCAS) or polyvinyl acetate phthalate, to which it is also possible to add, if desired, plasticizer (such as propylene glycol or triethyl citrate) and/or other additives and ancillary substances (e.g. buffers, bases, such as, preferably, aluminum hydroxide, or pigments).

[0042] In one embodiment of the invention the oral dosage form according to the invention comprises an enteric coating based on methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl - acrylate copolymer. Eudragit® L30D is particularly preferred (Eudragit® L30D is composed of methacrylic acid copolymer (type C) with molecular weight 250.000, sodium dodecylsulfate and polysorbate 80).

[0043] The layers are applied in conventional ways using equipment customary for these purposes.

[0044] The oral dosage form of the invention can be manufactured for example by processes known to the skilled worker for producing tablets and pellets (for example as disclosed in the various patent documents relating to oral dosage forms for proton pump inhibitors; the process mentioned in EP-A-0 519 365 or EP-A-0 244 380 may be mentioned by way of example).

[0045] Pellets can be obtained as the case may be by application of a preliminary isolation to sucrose starter pellets and subsequent application of a 10-20% suspension of the active compound in water with polyvinylpyrrolidone (PVP) as the binder.

[0046] The isolation layer can also be applied, analogously to tablets, using corresponding ready-made dispersions (e.g. opadry) in a fluidized bed coater. The coating with a layer, which is resistant to gastric juice, is carried out by a

procedure analogous to that for tablets, using fluidized bed technology.

[0047] In one embodiment of the invention, the pharmaceutical dosage form according to the invention is manufactured by producing a suspension of the magnesium salt of pantoprazole in an aqueous solution of PVP and spraying the suspension on a mixture of pharmaceutical excipients to form granules. In a preferred embodiment the PVP is low molecular weight PVP.

[0048] In the event of further processing the granules to enteric coated tablets the granules may be processed together with disintegrant and lubricant components by production processes familiar to the skilled worker to tablets and together with film former, plasticizer and coloring agent components obtaining the enteric coated tablets according to the invention.

[0049] Further subject of the invention is therefore a process for production of an oral dosage form in form of tablets or pellets containing the magnesium salt of pantoprazole comprising the following steps:

(a) production of a suspension of the magnesium salt of pantoprazole optionally together with further pharmaceutical excipients in an aqueous solution of PVP;
(b) providing a mixture of pharmaceutical excipients and
(c) granulation of the mixture obtained from (b) with the suspension obtained from (a).

[0050] In a preferred embodiment the PVP is low molecular weight PVP.

[0051] In case of dosage forms of the invention in form of tablets the granules obtained from (c) may be pressed after drying and mixing with lubricants and where applicable with further pharmaceutical excipients to tablets on a tableting machine and layered to form enteric coated tablets.

[0052] In case of dosage forms of the invention in form of multiparticulates the granules may be processed into pellets by extrusion and spheronization. Thereby the magnesium salt of pantoprazole can be suspended in the solution of PVP (a) and then mixed with other excipients (c). The mixture can be processed by extrusion/spheronization using suitable process equipments. The size of the obtained core pellets is approximately between 0.2 and 3 mm and preferably between 0.25 and 2 mm. In a preferred embodiment the PVP is low molecular weight PVP.

[0053] The manufactured extrusion pellets can further be layered with ingredients familiar to the skilled worker. The enteric coated pellets may be processed after drying by production processes familiar to the skilled worker to give enteric coated pellets which may be filled in capsules after mixing with glidants or pressed to tablets after mixing with further pharmaceutical excipients.

[0054] Alternatively, the suspension obtained from (a) may be sprayed on seeds (e.g. nonpareilles comprising sugar, cellulose or HPMC). The pellets obtained may be processed after drying by production process-ses familiar to the skilled worker to give enteric coated pellets which may be filled in capsules after mixing with glidants or pressed into tablets after mixing with further pharmaceutical excipients.

[0055] Particularly preferred the dosage forms of the invention in form of tablets are produced by granulating a mixture of mannitol and insoluble PVP with a suspension of the magnesium salt of pantoprazole, sodium carbonate and sodium dodecylsulfate in an aqueous solution of PVP, drying the granules, mixing with lubricant and pressing into tablets on a tableting machine, followed by the coating processes. In one embodiment the PVP is of low molecular weight.

[0056] Particularly preferred the dosage forms of the invention in form of multiparticulates based on nonpareilles-technology are produced by spraying a suspension of the magnesium salt of pantoprazole, sodium carbonate and sodium dodecylsulfate in an aqueous solution of PVP on starter pellets, drying the pellets, layering them with subcoating and enteric coating, mixing with glidants where applicable and filling into capsules. In a preferred embodiment the PVP is low molecular weight PVP.

[0057] In another embodiment which is also a particularly preferred dosage forms of the invention based on nonpareilles-technology the dosage form is produced by spraying a suspension of the magnesium salt of pantoprazole, sodium carbonate, pregelatinized starch and sodium dodecylsulfate in an aqueous solution of PVP on starter pellets, drying the pellets, layering them with subcoating and enteric coating, mixing with glidants where applicable and filling into capsules. In a preferred embodiment the PVP is low molecular weight PVP.

[0058] Particularly preferred the dosage forms of the invention in form of extrusion pellets are produced by granulating a mixture of microcrystalline cellulose, sodium carbonate, sodium starch glycolate, sodium carboxymethylcellulose with a suspension of the magnesium salt of pantoprazole in an aqueous solution of PVP, extruding the wet mass and rounding it using a spheronizer or marumerizer. The obtained pellet cores are dryed using a fluid bed dryer or other suitable drying techniques. Afterwards the pellets are layered with subcoating and gastric resistant coating, mixed with glidants where applicable and filled into capsules. In a preferred embodiment the PVP is low molecular weight PVP.

[0059] In an other embodiment of the invention the pharmaceutical form of the invention in form of tablets is produced by granulating a dry mixture of the magnesium salt of pantoprazole and pharmaceutical excipients with an aqueous solution of PVP, drying the granules and mixing them with further pharmaceutical excipients where applicable. The granules may be compressed into tablets on a tableting machine after mixing with further pharmaceutical excipients. Preferably the granulation is proceeded using a fluid bed granulator under convenient conditions. In a preferred embod-

iment the PVP is low molecular weight PVP.

[0060] Subject of the invention is therefore also a process to produce an oral dosage form in form of tablets or multiparticulates containing the magnesium salt of pantoprazole comprising the following steps:

(a) production of a dry mixture of the magnesium salt of pantoprazole and pharmaceutical excipients and
(b) granulating the mixture obtained from (a) with an aqueous solution of PVP.

[0061] In a preferred embodiment the PVP is low molecular weight PVP.

[0062] In case of dosage forms of the invention in form of extrusion pellets the aforementioned mixture may be processed into pellets by extrusion and spheronization. Thereby the magnesium salt of pantoprazole can be mixed with other excipients (a) and granulated with an aqueous solution of PVP (b). In a preferred embodiment the PVP is low molecular weight PVP. The mixture can be processed by extrusion/spheronization using suitable process equipments. The size of the obtained core pellets is approximately between 0.2 and 3 mm and preferably between 0.25 and 2 mm.

[0063] Particularly preferred the dosage forms of the invention in form of tablets are produced by granulating a mixture of the magnesium salt of pantoprazole, mannit and sodium carbonate and insoluble PVP using an aqueous solution of PVP, drying the granules, mixing with lubricants and pressing into tablets on a tableting machine, followed by the coating processes. In a preferred embodiment the PVP is low molecular weight PVP.

[0064] Particularly preferred the dosage forms of the invention in form of extrusion pellets are produced by granulating a dry mixture of microcrystalline cellulose, sodium carbonate, sodium starch glycolate, sodium carboxymethylcellulose and the magnesium salt of pantoprazole with an aqueous solution of PVP, extruding the wet mass and rounding it using a spheronizer or marumerizer. The obtained pellet cores are dryed using a fluid bed dryer or other suitable drying techniques, followed by the above mentioned coating processes. In a preferred embodiment the PVP is low molecular weight PVP.

Description of the figures

Figure 1

[0065] Figure 1 shows the release of the magnesium salt of pantoprazole from tablet cores containing different types of PVP with different molecular weights. The granules of example B9 were produced by granulating them using a suspension of the magnesium salt of pantoprazole in an aqueous solution of PVP. The granules of the examples B8, B10, B11, B12 and the reference example C1 were produced by granulating a dry mixture of the magnesium salt of pantoprazole and pharmaceutical excipients using an aqueous solution of PVP.

Figure 2

[0066] Figure 2 shows the difference in release of the magnesium salt of pantoprazole from a tablet compared to the release of the sodium salt of pantoprazol from a tablet with comparable composition.

[0067] The production of dosage forms according to the invention is described by way of example below. The following examples explain the invention in more detail without restricting it.

Examples

A. Synthesis of Magnesium bis[5-[difluoromethoxy]-2-[[3,4-dimethoxy-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazolide] dihydrate

[0068] 3.85 kg (8.9 mol) of pantoprazole Na sesquihydrate [sodium [5-[difluoromethoxy]-2-[[3,4-dimethoxy-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazolide]sesquihydrate] are dissolved at 20-25°C in 38.5 l of purified water in a stirring vessel. A solution of 1.0 kg (4.90 mol) of magnesium dichloride hexahydrate in 8 l of purified water is added with stirring at 20-30°C in the course of 3 to 4 h. After stirring for a further 18 h, the precipitated solid is centrifuged, washed with 23 l of purified water, stirred at 20-30°C for 1 to 2 h in 35 l of purified water, centrifuged again and washed again with 30-50 l of purified water. The solid product is dried at 50°C in vacuo (30-50 mbar) until a residual water content of < 4.8% is achieved. The product is then ground.

[0069] The title compound is obtained as a white to beige powder, which is employed directly for further pharmaceutical processing.

[0070] Yield: 3.40 kg (90% of theory); water content: 4.5-4.6%; melting point: 194-196 °C with decomposition.

CHN analysis	C	H	N	S
Theory	46.58	3.91	10.19	7.77
Found	46.33	3.89	10.04	7.83

[0071] Alternatively the title compound can be produced using mixtures of organic solvents with water. For this, pantoprazole Na sesquihydrate is dissolved in an organic solvent at 50-60°C. 0.5 mole equivalents of the magnesium salt (e. g. magnesium chloride hexahydrate), dissolved in water, are added drop by drop and the solution is allowed to cool with stirring. The precipitated solid is filtered off, washed with the corresponding organic solvent and is dried in vacuo at 50°C to constant weight. The title compound is obtained as a colourless powder. Examples for different solvents are given in the following table 1.

Table 1:

pantoprazole Na sesquihydrate	organic solvent	water	yield of title compound	melting point °C	water content %
50 g	isopropanol 300 ml	300 ml	45,4 g	196 - 197	4,4 - 4,5
50 g	isopropanol 300 ml	120 ml	45,9 g	196 - 197	4,3
50 g	ethanol 300 ml	300 ml	45,8 g	197 - 198	4,6
50 g	aceton 300 ml	300 ml	45,6 g	195 - 196	4,6, - 4,7

[0072] Alternatively the title compound can be produced by reacting pantoprazole with a basic magnesium salt, such as magnesium methylate, for example in the following manner: 90 g of pantoprazole are dissolved in 700 ml of 2-propanol at 60-70°C. 13.4 g (0.5 moles) of solid magnesium methylate are added, the solution is allowed to cool with stirring and filtered. After addition of 36 ml of water the crystalline solid formed is filtered off, washed with water and dried in vacuo at 50°C to constant weight. The title compound of melting point 194-196°C (water content 4.8 %) is obtained as beige solid.

B. Production of dosage forms according to the invention

Example B.1

[0073] Pellets made by Wurster coating (Nonpareilles):

I. Active pellets:	
a.) Sucrose starter pellets (0.425-0.5 mm)	500.0 g
b.) Sodium carbonate	30.0 g
c.) Pantoprazole-Mg dihydrate	300.0 g
d.) Polyvinylpyrrolidone K 25	35.0 g
II. Intermediate layer (subcoating):	
e.) Hydroxypropylmethylcellulose	120.0 g
f.) Titanium dioxide	2.0 g
g.) LB Iron oxide yellow	0.2 g
h.) Propylene glycol	24.0 g
III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
i.) Eudragit® L 30 D	230.0 g

(continued)

II. Intermediate layer (subcoating):	
j.) Triethyl citrate	7.0 g
a. is sprayed with an aqueous dispersion of b., c. and d. in a fluidised bed process (Wurster equipment) or other suitable equipments (e.g. coating pan). e. is dissolved in water (A). f. and g. are suspended in water using a high shear mixer (B). A and B are combined and after addition of h. the resulting suspension is sieved through a suitable sieve. The suspension is sprayed onto 500 g of the active pellets obtained under I using a fluidised bed process (Wurster) or other suitable processes (e.g. coating pan). i. is suspended in water and after addition of j. the resulting dispersion is sieved through a suitable sieve. II is sprayed onto 500 g of the isolated pellets obtained under II in a Wurster fluidised bed-apparatus or other suitable equipments (e.g. coating pan).	

[0074] The resulting enteric coated pellets could be filled in hard gelatine capsules of suitable size (e.g. size 2) or tableted using suitable tableting ingredients (e.g. microcrystalline cellulose or lactose monohydrate) on a prevalent tablet press (see examples B6/7).

Example B.2

[0075] Pellets made by Wurster coating (Nonpareilles):

I. Active pellets:	
a.) Cellulose pellets (0.6-0.7 mm)	1000.0 g
b.) Sodium carbonate	75.0 g
c.) Pantoprazole-Mg dihydrate	650.0 g
d.) Polyvinylpyrrolidone K 25	80.0 g
II. Intermediate layer (subcoating):	
e.) Hydroxypropylmethylcellulose	250.0 g
f.) Titanium dioxide	5.0 g
g.) LB Iron oxide yellow	0.45 g
III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
h.) Eudragit® L 30 D	365.0 g
i.) Triethyl citrate	15.0 g
a. is sprayed with an aqueous dispersion of b., c. and d. in a fluidised bed process (Wurster equipment) or other suitable equipments (e.g. coating pan). e. is dissolved in water (A). f. and g. are suspended in water using a high shear mixer (B). A and B are combined and the resulting suspension is sieved through a suitable sieve. The suspension is sprayed onto 1000 g of the active pellets obtained under I using a fluidised bed process (Wurster) or other suitable processes (e.g. coating pan).	

h. is suspended in water and after addition of i. the resulting dispersion is sieved through a suitable sieve. III is sprayed onto 1000 g of the isolated pellets obtained under II in a Wurster fluidised bed-apparatus or other suitable equipments (e.g. coating pan).

[0076] The resulting enteric coated pellets could be filled in hard gelatine capsules of suitable size (e.g. size 2) or tableted using suitable tableting ingredients (e.g. microcrystalline cellulose or lactose monohydrate) on a prevalent tablet press (see examples B6/7).

Example B.3

[0077] Pellets made by Wurster coating (Nonpareilles):

I. Active pellets:	
a.) Cellulose pellets (0.4-0.5 mm)	2000.0 g
b.) Sodium carbonate	136.0 g
c.) Pantoprazole-Mg dihydrate	1420.0 g
d.) Polyvinylpyrrolidone K 25	117.0 g
e.) Sodium dodecylsulfate (SDS)	16.4 g
II. Intermediate layer (subcoating):	
f.) Hydroxypropylmethylcellulose	600.0 g
g.) Polyvinylpyrrolidone K 25	8.0 g
h.) Titanium dioxide	10.0 g
i.) LB Iron oxide yellow	1.0 g
To produce core material, suspension layering is performed in a fluid bed apparatus or other suitable equipment as described in example B1.	

[0078] The pellets covered with intermediate layer are produced as described in example B1.

III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
j.) Hydroxypropylmethylcellulose acetate succinate	800.0 g
k.) Triethyl citrate	250.0 g
l.) Ethanol	7250.0 g

[0079] The enteric coating layer is applied to the isolated pellets using fluidized bed equipment from a water/ethanol solution.

[0080] The resulting enteric coated pellets could be filled in hard gelatine capsules of suitable size (e.g. size 2) or tableted using suitable tableting ingredients (e.g. microcrystalline cellulose or lactose monohydrate) on a prevalent tablet press (see examples B6/7).

Example B.4

[0081] Pellets made by extrusion/spheronization:

I. Manufacture of pellets using extrusion/spheronization:	
a.) Pantoprazole-Mg dihydrate	250.0 g
b.) Microcrystalline cellulose	150.0 g
c.) Sodium starch glycolate	20.0 g
d.) Sodium carbonate	32.5 g
e.) Sodium carboxymethylcellulose	25.0 g
f.) Polyvinylpyrrolidone K 25	35.0 g
a.-c. are mixed using a suitable mixer. d.-f. are dissolved in water and the resulting binder solution is added to the powder mixture. After addition of the solution and mixing the mass is extruded using a screw extruder. Afterwards the granules are rounded using a spheronizer and dryed in a fluidised bed apparatus.	

II. Intermediate layer (subcoating):

[0082] The application of the intermediate layer is carried out by a procedure analogus to that described for the nonpareilles pellets (example B1 to B3) using fluidised bed or other suitable equipment.

III. Coating with a layer which is resistant to gastric juice:

[0083] The application of the gastric resistant layer is carried out by a procedure analogus to that described for the nonpareilles pellets (example B1 to B3) using fluidised bed or other suitable equipment.

[0084] The resulting enteric coated pellets could be filled in hard gelatine capsules of suitable size (e.g. size 2) or tableted using suitable tableting ingredients (e.g. microcrystalline cellulose or lactose monohydrate) on a prevalent tablet press (see examples B6/7).

Example B.5

[0085] Pellets made by extrusion/spheronization:

I. Manufacture of pellets using extrusion/spheronization:	
a.) Pantoprazole-Mg dihydrate	1300.0 g
b.) Microcrystalline cellulose	700.0 g
c.) Lactose monohydrate	150.0 g
d.) Hydroxypropylmethylcellulose	110.0 g
e.) Sodium carbonate	180.0 g
f.) Pregelatinized starch	125.0 g
g.) Polyvinylpyrrolidone K 25	200.0 g

[0086] The extrusion pellets are produced as described in example B4.

II. Intermediate layer (subcoating):

[0087] The application of the intermediate layer is carried out by a procedure analogus to that described for the nonpareilles pellets (example B1 to B3) using fluidised bed or other suitable equipment.

III. Coating with a layer which is resistant to gastric juice:

[0088] The application of the gastric resistant layer is carried out by a procedure analogus to that described for the nonpareilles pellets (example B1 to B3) using fluidised bed or other suitable equipment.

[0089] The resulting enteric coated pellets could be filled in hard gelatine capsules of suitable size (e.g. size 2) or tableted using suitable tableting ingredients (e.g. microcrystalline cellulose or lactose monohydrate) on a prevalent tablet press (see examples B6/7).

Example B.6

[0090] Multiple unit tableted dosage form made from Nonpareilles-Pellets:

I. Active pellets:	
a.) Cellulose pellets (0.6-0.7 mm)	2500.0 g
b.) Sodium carbonate	180.0 g
c.) Pantoprazole-Mg dihydrate	1700.0 g
d.) Polyvinylpyrrolidone K 25	250.0 g
e.) Sodium dodecylsulfate	18.0 g
II. Intermediate layer (subcoating):	
f.) Hydroxypropylmethylcellulose	600.0 g

(continued)

II. Intermediate layer (subcoating):	
g.) Talcum (micronized)	100.0 g
h.) Magnesium stearate	80.0g
III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
i.) Methacrylic acid copolymer	925.0 g
j.) Polyethylene glycole 400	28.0 g
a. is sprayed with an aqueous dispersion of b., c., d. and e. in a fluidized bed process (Wurster equipment) or other suitable equipments (e.g. coating pan). f. is dissolved in water (A). g. and h. are suspended in water using a high shear mixer (B). A and B are combined and the resulting suspension is sieved through a suitable sieve. The suspension is sprayed onto 2500 g of the active pellets obtained under I using a fluidised bed process (Wurster) or other suitable processes (e.g. coating pan). i. is suspended in water and after addition of j. the resulting dispersion is sieved through a suitable sieve. III is sprayed onto 2500 g of the isolated pellets obtained under II in a Wurster fluidised bed-apparatus or other suitable equipments (e.g. coating pan).	

IV. Tablets:

[0091]

k.) Microcrystalline cellulose	3750.0 g
l.) Crosslinked polyvinylpyrrolidone	100.0 g
m.) Magnesium stearate	7.0 g

2500 g of enteric coated pellets are mixed with the tableting excinpients and compressed into tablets using a single punch tableting machine equipped with 11 mm round punches. The amount of pantoprazole is approx. 20 mg.

Example B.7

[0092] Multiple unit tableted dosage form made from Extrusion-Pellets:

I. Manufacture of pellets using extrusion/spheronization:	
a.) Pantoprazole-Mg dihydrate	433.0 g
b.) Microcrystalline cellulose	240.0 g
c.) Lactose monohydrate	55.0 g
d.) Hydroxypropylmethylcellulose	35.0 g
e.) Sodium carbonate	60.0 g
f.) Sodium dodecylsulfate	5.5 g
g.) Pregelatinized starch	35.0 g
h.) Polyvinylpyrrolidone K 25	70.0 g
II. Intermediate layer (subcoating):	
i.) Hydroxypropylmethylcellulose	190.0 g
j.) Polyvinylpyrrolidone K 25	8.0 g
j.) Talcum (micronized)	32.0 g

(continued)

II. Intermediate layer (subcoating):	
k.) Magnesium stearate	14.0g
The extrusion pellets are produced as described in example B5.	

The application of the intermediate layer is carried out by a procedure analogus to that described for the nonpareilles pellets (example B1 to B3) using fluidised bed or other suitable equipment.

III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
l.) Methacrylic acid copolymer	296.0 g
m.) Glycerol triacetate	28.0 g

The application of the gastric resistant layer is carried out by a procedure analogus to that described for the nonpareilles pellets (example B1 to B3) using fluidised bed or other suitable equipment.

[0093] IV. Tablets:

n.) Microcrystalline cellulose	1200.0 g
o.) Crosslinked polyvinylpyrrolidone	32.0 g
p.) Polyethyleneglycole 4000	38.0 g
q.) Magnesium stearate	4.5 g

The enteric coated extrusion pellets are tableted with the above tableting excipients as described in example B6 of an amount of approximately 40 mg pantoprazole.

Example B.8

Tablets:

[0094]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Mannitol	52.66 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 25	5.00 mg
f.) Purified water	7.42 mg
g.) Calcium stearate	3.00 mg
II. Intermediate layer (subcoating):	
h.) Hydroxypropylmethylcellulose	11.87 mg
i.) Polyvinylpyrrolidone K 25	0.24 mg
j.) Titanium dioxide	0.21 mg
k.) LB Iron oxide yellow	0.02 mg
l.) Propylene glycol	2.66 mg
III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
m.) Eudragit® L 30 D	7.27 mg

(continued)

III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
n.) Triethyl citrate	0.73 mg
a. is dry-mixed with a part of b., a part of c. and d. and put in the vessel of a fluid bed granulator; e. is dissolved in f. together with the other part of b. and c. to form the granulation liquid. The solution is sprayed on the mixture under convenient conditions. After drying and mixing with g. the mixture is pressed into tablets using a rotary tableting machine equipped with 7 mm round punches. Tablet weight is approx. 156.7 mg, corresponding to 40 mg pantoprazole (i.e. 43.04 mg pantoprazole-Mg dihydrate). h. is dissolved in water (A). j. and k. are suspended in a solution of i. in water using a high shear mixer (B). After sieving of B, A and B are combined I. is added to the suspension. The suspension is sprayed onto the tablet cores obtained under I using a coating pan. n. is suspended in water and mixed m. III is sprayed onto the isolated tablets obtained under II using a coating pan.	

Example B.9

Tablets:

[0095]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Mannitol	51.94 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 25	5.00 mg
f.) Sodium dodecylsulfate	0.72 mg
g.) Purified water	7.42 mg
h.) Calcium stearate	3.00 mg
f. and a part of b. are dissolved in water, a part of c. is added and a. is suspended in the solution. A solution of e. in water is added to the suspension. The other part of b. and c. is mixed with d. and the mixture is put in the vessel of a fluid bed granulator. The suspension is sprayed on the mixture under convenient conditions. After drying and mixing with h. the mixture is compressed into tablets using a rotary tableting machine equipped with 7 mm round punches. Tablet weight is approx. 156.7 mg.	

[0096] The tablet cores are isolated and layered with an enteric coating as described in Example B8.

Example B.10

Tablets:

[0097]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Mannitol	52.66 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 30	5.00 mg
f.) Purified water	7.42 mg
g.) Calcium stearate	3.00 mg

The tablet cores are produced as described in example B8.
The tablet cores are layered with an isolating coating and an enteric coating as described in example B8.

Example B.11

Tablets:

[0098]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Mannitol	52.66 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 17	5.00 mg
f.) Purified water	7.42 mg
g.) Calcium stearate	3.00 mg

The tablet cores are produced as described in example B8.
The tablet cores are layered with an isolating coating and an enteric coating as described in example B8.

Example B.12

Tablets:

[0099]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Mannitol	52.66 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 12	5.00 mg
f.) Purified water	7.42 mg
g.) Calcium stearate	3.00 mg

The tablet cores are produced as described in example B8.
The tablet cores are layered with an isolating coating and an enteric coating as described in example B8.

Example B.13

Tablets:

[0100]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Lactose	55.00 mg
d.) Crospovidone	35.00 mg
e.) Polyvinylpyrrolidone K 25	5.00 mg
f.) Purified water	7.42 mg
g.) Calcium stearate	3.00 mg

The tablet cores are produced as described in example B8. Tablet weight approx. 154 mg.

II. Intermediate layer (subcoating):	
h.) Hydroxypropylmethylcellulose	12.20 mg
i.) Titanium dioxide	0.21 mg
j.) LB Iron oxide yellow	0.02 mg
h. is dissolved in water (A). i. and j. are suspended in water using a high shear mixer (B). A and B are combined and the resulting suspension is sieved through a suitable sieve. The suspension is sprayed onto the tablet cores obtained under I using a coating pan.	

[0101] The isolated tablet cores are layered with an enteric coating as described in example B8.

Example B.14

Tablets:

[0102]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Trinatriumphosphate	5.55 mg
c.) Mannitol	55.00 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 25	5.00 mg
f.) Purified water	7.42 mg
g.) Magnesium stearate	3.00 mg

[0103] The tablet cores are produced as described in example B8. Tablet weight approx. 159 mg.

II. Intermediate layer (subcoating):

[0104] The tablet cores are layered with an isolating coating as described in example B8.

III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
m.) Methacrylic acid copolymer	6.5 mg
n.) Glycerol triacetate	0.65 mg

The application of the gastric resistant layer is carried out as described in example B8.

Example B.15

[0105]

I. Tablet core	
a) Pantoprazole-Mg dihydrate	43,04 mg
b) Sodium carbonate	5,55 mg
c) Mannitol	52,66 mg
d) Crospovidone	40,00 mg
e) PVP 90 (povidone)	5,00 mg
f) Calcium stearate	3,00 mg
a) is mixed with some of b), c) and the complete amount of d). The remainders of b) and c) are added to a clear aqueous solution of e). Granules are obtained with this solution in a fluidized bed. f) is added to the dry granules and the granules are pressed on a suitable tablet- press.	

II. Preliminary isolation (intermediate layer)	
g) HPMC 2910, 3 cps	11,87 mg
h) PVP 25	0,24 mg
i) Titanium dioxide	0,21 mg
j) Iron oxide yellow 100 E 172	0,02 mg
k) Propylene glycol	2,66 mg
Total weight per preisolated core	172 mg
III. Coating with a layer which is resistant to gastric juice	
l) Eudragit L 30 D	7,27 mg
m) Triethyl citrate	0,73 mg
Total weight per film-coated tablet resistant to gastric juice	180 mg
g) is dissolved in water and h) is added and also dissolved (A). i) and j) are suspended in water using a suitable stirrer (B). A and B are combined. After addition of k), the suspension is sieved immediately before further processing, during which the tablet cores obtained under I. are coated to an adequate thickness of the intermediate layer in a suitable coating apparatus. l) is diluted with water and m) is added. The dispersion is sieved before processing.	

[0106] The preisolated tablets are sprayed in suitable coating apparatuses using the obtained dispersion.

Example B.16

[0107] Pellets made by Wurster coating (Nonpareilles):

I. Active pellets:	
a.) Sucrose starter pellets (0.71-0.85 mm)	4.0 kg
b.) Sodium carbonate	0.27 kg
c.) Pantoprazole-Mg dihydrate	2.84 kg
d.) Polyvinylpyrrolidone K 25	0.23 kg
e.) Pregelatinized starch	0.22 kg
f.) Sodium dodecylsulfate	0.03 kg
a. is sprayed with an aqueous dispersion of the other ingredients in a fluidised bed process (Wurster equipment) or other suitable equipments (e.g. coating pan).	

II. Intermediate layer (subcoating):	
g.) Hydroxypropylmethylcellulose	1.830 kg
h.) Titanium dioxide	0.028 kg
i.) LB Iron oxide yellow	0.003 kg
j.) Polyvinylpyrrolidone K25	0.021 kg
g. and j. are dissolved in water (A). h. and i. are suspended in water using a high shear mixer (B). A and B are combined and the resulting suspension is sieved through a suitable sieve. The suspension is sprayed onto the active pellets obtained under I using a fluidised bed process (Wurster) or other suitable processes (e.g. coating pan).	

III. Coating with a layer which is resistant to gastric juice (Enteric coating):	
k.) Eudragit® L 30 D	4.40 kg
l.) Triethyl citrate	0.13 kg
m.) Talcum	0.06 kg
k. is suspended in water and after addition of l. the resulting dispersion is sieved through a suitable sieve. The dispersion is sprayed on the isolated pellets obtained under II in a Wurster fluidised bed-apparatus or other suitable equipments (e.g. coating pan).	

[0108] The resulting enteric coated pellets are mixed with talcum (m) und could be filled in hard gelatine capsules of suitable size (e.g. size 2) or tableted using suitable tableting ingredients (e.g. microcrystalline cellulose or lactose monohydrate) on a prevalent tablet press.

C. Physical investigations and comparative tests with dosage forms in which high molecular weight PVP was used as binder

Example C.1

Tablets:

[0109]

I. Tablet Core:	
a.) Pantoprazole-Mg dihydrate	43.04 mg
b.) Sodium carbonate	5.55 mg
c.) Mannitol	52.66 mg
d.) Crospovidone	40.00 mg
e.) Polyvinylpyrrolidone K 90	5.00 mg
f.) Purified water	7.42 mg
g.) Magnesium stearate	3.00 mg

The tablet cores are produced as described in example B8.
The tablet cores are layered with an isolating coating and an enteric coating as described in example B8.

Example C.2

[0110]

I. Tablet core	
a) Pantoprazole-Na sesquihydrate	45,10 mg
b) Sodium carbonate	10,00 mg
c) Mannitol	42,70 mg
d) Crospovidone	50,00 mg
e) PVP 90 (povidone)	4,00 mg
f) Calcium stearate	3,20 mg
a) is mixed with some of b), c) and d). The remainders of b) and c) are added to a clear aqueous solution of e). Granules are obtained with this solution in a fluidized bed. The remainder of d) and f) are added to the dry granules and the granules are pressed on a suitable tablet press.	

II. Preliminary isolation (intermediate layer)	
g) HPMC 2910, 3 cps	19,00 mg
h) PVP 25	0,38 mg
i) Titanium dioxide	0,34 mg
j) Iron oxide yellow 100 E 172	0,03 mg
k) Propylene glycol	4,25 mg
Total weight per preisolated core	188 mg
III. Coating with a layer which is resistant to gastric juice	
l) Eudragit L 30 D	14,56 mg
m) Triethyl citrate	1,45 mg

(continued)

III. Coating with a layer which is resistant to gastric juice	
Total weight per film-coated tablet resistant to gastric juice	204 mg
g) is dissolved in water and h) is added and also dissolved (A). i) and j) are suspended in water using a suitable stirrer (B). A and B are combined. After addition of k), the suspension is sieved immediately before further processing, during which the tablet cores obtained under I. are coated to an adequate thickness of the intermediate layer in a suitable coating apparatus.	
l) is diluted with water and m) is added. The dispersion is sieved before processing.	

[0111] The preisolated tablets are sprayed in suitable coating apparatuses using the obtained dispersion.

[0112] The release of the magnesium salt of pantopazole was determined for tablet cores corresponding to example B8, B9, B10, B11 and B12 compared to a tablet core corresponding to example C1.

[0113] Disintegration of tablet cores: the disintegration of tablet cores was determined as described in the European Pharmacopoeia.

[0114] Release of active ingredient: the release of active ingredient was determined as described in the US Pharmacopoeia (USP XXV; apparatus 2; phosphate buffer pH 6.8; 100 rpm).

[0115] The release of the formulations according to example B15 and C2 was determined after 2 hours in 0.1 N hydrochloric acid and 1 hour in phosphate buffer pH 6.8; 100 rpm). In Figure 2 only the drug release in phosphate buffer is shown.

[0116] Result: The disintegration results are shown in Table 1, the dissolution profiles are shown in Figure 1.

Table 1

Example	PVP used as binder	Disintegration [min]
B8	PVP 25	7
B9	PVP 25	6.5
B10	PVP 30	10.5
B11	PVP 17	9
B12	PVP 12	7.5
C1	PVP 90	10.5

[0117] Surprisingly, the dissolution of the magnesium salt of pantoprazole from tablet cores in which low molecular weight PVP was used as binder is faster than from tablet cores in which high molecular weight PVP was used although the disintegration for all tablet cores is below 15 minutes.

D. Physical investigations and comparative tests with dosage forms contaning pantoprazole sodium sesquihydrate and pantoprazole magnesium dihydrate

[0118] Figure 2 shows the difference in release of the magnesium salt of pantoprazole from a tablet compared to the release of the sodium salt of pantoprazol from a tablet with comparable composition. The dosage form having the sodium salt of pantoprazole as active ingredient (example C.2) shows after a short lag time an immediate and complete release of the active ingredient. Surprisingly the dosage form containing the magnesium salt of pantoprazole does not have a lag time in release of active compound and shows a constant release of active ingredient over whole period.

E. Results of Clinical Study

[0119] Healing of patient suffering from GERD (gastro-oesophageal reflux disease) I to III (according to Savary/Miller classification modified by Siewert) after treatment with pantoprazole magnesium dihydrate 40 mg o.d. (dosage form according to the invention) in comparision with a corresponding pantoprazole sodium sesquihydrate 40 mg o.d. dosage form have been studied. Surprisingly it has been found that pantoprazole magnesium dihydrate formulation is superior to pantoprazole sodium sesquihydrate formulation in the healing of GERD I to III, whereby safety is comparable for both dosage forms.

Industrial applicability

[0120] The dosage forms according to the invention containing the magnesium salt of pantoprazole can be employed for the treatment and prevention of all the diseases, which are regarded as treatable or avoidable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, such dosage forms according to the invention can be employed in the treatment of stomach disorders. Examples which may be mentioned in connection with the invention are the treatment or prophylaxis of benign gastric ulcer, gastro-oesophageal reflux disease, Zollinger-Ellison syndrome, duodenal ulcer, duodenal ulcer associated with Helicobacter pylori, prophylaxis of NSAID-associated gastric or duodenal ulcer in patients with an increased risk of gastroduodenal complication who require continued NSAID treatment or combination therapy with antibiotics in the eradication of Helicobacter pylori. Such dosage forms according to the invention contain between 1 and 500 mg, preferably between 5 and 100 mg, particularly preferable between 5 and 80 mg of the pantoprazole. Examples which may be mentioned are tablets or capsules, which contain the pantoprazole magnesium salt in an amount corresponding to 10, 20, 40, 50, 80 or 100 mg of pantoprazole (free acid). The administration of the daily dose (e.g. 40 mg of active compound) can be carried out, for example, in the form of an individual dose or by means of a number of doses of the administration forms according to the invention (e.g. 2 times 20 mg of active compound).

[0121] The invention therefore also relates to a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a proton pump inhibitor is indicated, which comprises administration of a therapeutically effective amount pantoprazole magnesium in a dosage form according to the invention. In one embodiment the clinical condition is selected from the group of benign gastric ulcer, gastro-oesophageal reflux disease, Zollinger-Ellison syndrome, duodenal ulcer, duodenal ulcer associated with Helicobacter pylori, prophylaxis of NSAID-associated gastric or duodenal ulcer in patients with an increased risk of gastroduodenal complication who require continued NSAID treatment and combination therapy with antibiotics in the eradication of Helicobacter pylori. In a preferred embodiment the clinical condition is gastro-oesophageal reflux disease (GERD), in particular GERD I to III (according to Savary/Miller classification, optionally modified according to Siewert).

[0122] The dosage forms according to the invention can be combined with other medicaments, either in various combinations or in a fixed combination. In connection with the administration forms according to the invention, which contain magnesium salt of pantoprazole as active compounds, combinations with antimicrobial active compounds and combinations with NSAIDs (nonsteroidal antiinflammatory drugs) are particularly worthy of mention. Combination with antimicrobial agents, such as are employed for the control of the microorganism Helicobacter pylori (H. pylori), may particularly be mentioned.

[0123] Examples of suitable antimicrobial active compounds (active against Helicobacter pylori) are described in EP-A-0 282 131. Examples of antimicrobial agents suitable for the control of the microorganism Helicobacter pylori which may be mentioned are, for example, bismuth salts [e.g. bismuth subcitrate, bismuth subsalicylate, ammonium bismuth (III) potassium citrate dihydroxide, bismuth nitrate oxide, dibismuth tris(tetraoxodialuminate)], but in particular β-lactam antibiotics, for example penicillins (such as benzylpenicillin, phenoxymethylpenicillin, propicillin, azidocillin, dicloxacillin, flucloxacillin, oxacillin, amoxicillin, bacampicillin, ampicillin, mezlocillin, piperacillin or azlocillin), cephalosporins (such as cefadroxil, cefaclor, cefalexin, cefixime, cefuroxime, cefetamet, cefadroxil, ceftibuten, cefpodoxime, cefotetan, cefazolin, cefoperazon, ceftizoxime, cefotaxime, ceftazidime, cefamandol, cefepime, cefoxitin, cefodizime, cefsulodin, ceftriaxon, cefotiam or cefmenoxime) or other β-lactam antibiotics (e.g. aztreonam, loracarbef or meropenem); enzyme inhibitors, for example sulbactam; tetracyclines, for example tetracycline, oxytetracycline, minocycline or doxycycline; aminoglycosides, for example tobramycin, gentamicin, neomycin, streptomycin, amikacin, netilmicin, paromomycin or spectinomycin; amphenicols, for example chloramphenicol or thiamphenicol; lincomycins and macrolide antibiotics, for example clindamycin, lincomycin, erythromycin, clarithromycin, spiramycin, roxithromycin or azithromycin; polypeptide antibiotics, for example colistin, polymixin B, teicoplanin or vancomycin; gyrase inhibitors, for example norfloxacin, cinoxacin, ciprofloxacin, pipemidic acid, enoxacin, nalidixic acid, pefloxacin, fleroxacin or ofloxacin; nitroimidazoles, for example metronidazole; or other antibiotics, for example fosfomycin or fusidic acid. Particularly worthy of mention in this connection is the administration of the magnesium salt of pantoprazole with the combination of a multiplicity of antimicrobial active compounds, for example with the combination of a bismuth salt and/or tetracyclines with metronidazole or the combination of amoxicillin or clarithromycin with metronidazole and amoxicillin with clarithromycin.

Claims

1. A solid dosage form in tablet or pellet form for oral administration of pantoprazole magnesium dihydrate comprising a therapeutically effective amount of the pantoprazole magnesium dihydrate together with low molecular weight polyvinylpyrrolidone and pharmaceutically acceptable excipients.

2. Dosage form according to claim 1, which is a delayed release dosage form comprising an enteric layer, which is

soluble in neutral or alkaline conditions and at least one intermediate layer (subcoating layer).

3. Dosage form according to claim 1 or 2, which is an orally administerable medicament in pellet or tablet form which is resistant to gastric juice, and in which each pellet or tablet consists of a core in which active compound or its physiologically-tolerated salt is in admixture with binder, filler and, optionally, a member selected from the group consisting of another tablet auxiliary and a basic physiologically-tolerated inorganic compound, an inert water-soluble intermediate layer surrounding the core and an outer layer which is resistant to gastric juice, wherein the active compound is pantoprazole magnesium dihydrate, the binder is low molecular weight polyvinylpyrrolidone and/or hydroxypropylmethylcellulose and, optionally, the filler is mannitol.

4. Dosage form according to claim 3, wherein pharmacologically tolerated alkali metal, alkaline earth metal or earth metal salt of a weak acid or pharmacologically tolerated hydroxide or oxide of an alkaline earth or earth metal is the basic, physiologically tolerated inorganic compound.

5. Dosage form according to any of claims 1 to 4, comprising the pantoprazole magnesium dihydrate together with low molecular weight polyvinylpyrrolidone in an alkaline pellet or tablet core.

6. Dosage form according to any of claims 1 to 5 in tablet form, comprising as excipients for the tablet core sodium carbonate, mannitol, crospovidone, low molecular weight polyvinylpyrrolidone, and magnesium or calcium stearate.

7. Dosage form according to any of claims 1 to 6 in pellet form, comprising a pellet core, an intermediate layer and an enteric coating, wherein the pellet core is formed from starter pellets, pantoprazole magnesium dihydrate, starch and optionally other excipients.

8. Dosage form according to claim 7 in pellet form, comprising a pellet core an intermediate layer and an enteric coating, wherein the pellet core is formed from sucrose starter pellets, pantoprazole magnesium dihydrate, sodium carbonate, PVP 25, pregelatinized starch and sodium dodecylsulfate, the intermediate layer is formed of HPMC, PVP 25, titanium dioxide and iron oxide yellow, and the enteric coating is formed of Eudragit L 30 D and triethyl citrate.

9. Dosage form according to any of claims 1 to 8 containing between 5 and 100 mg of pantoprazole magnesium dihydrate.

10. Dosage form according to claim 9, which contains an amount of pantoprazole magnesium dihydrate, which corresponds to 10, 20, 40, 50, 80 or 100 mg of pantoprazole (free acid).

11. Dosage form according to claim 10, which contains an amount of pantoprazole magnesium dihydrate, which corresponds to 40 or 80 mg of pantoprazole (free acid).

12. Use of the dosage form according to any of claims 1 to 11 for the manufacture of a medicament for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a proton pump inhibitor is indicated.

13. Use according to claim 12, wherein the clinical condition is selected from the group of benign gastric ulcer, gastro-oesophageal reflux disease, Zollinger-Ellison syndrome, duodenal ulcer, duodenal ulcer associated with Helicobacter pylori, prophylaxis of NSAID-associated gastric or duodenal ulcer in patients with an increased risk of gastroduodenal complication who require continued NSAID treatment and combination therapy with antibiotics in the eradication of Helicobacter pylori.

14. Use according to claim 13, wherein the clinical condition is gastro-oesophageal reflux disease (GERD).

15. Use according to claim 14, wherein the clinical condition is GERD I to III (according to Savary/Miller Classification).

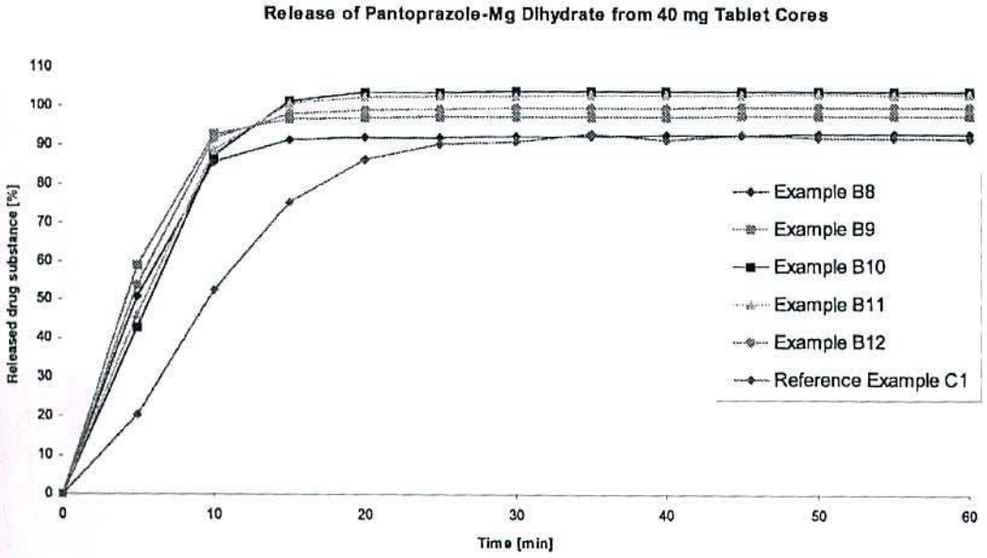

Release of Pantoprazole-Mg Dihydrate from 40 mg Tablet Cores
Released drug substance [%]
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Time [min]
Example B8
Example B9
Example B10
Example B11
Example B12
Reference Example C1

Figure 1

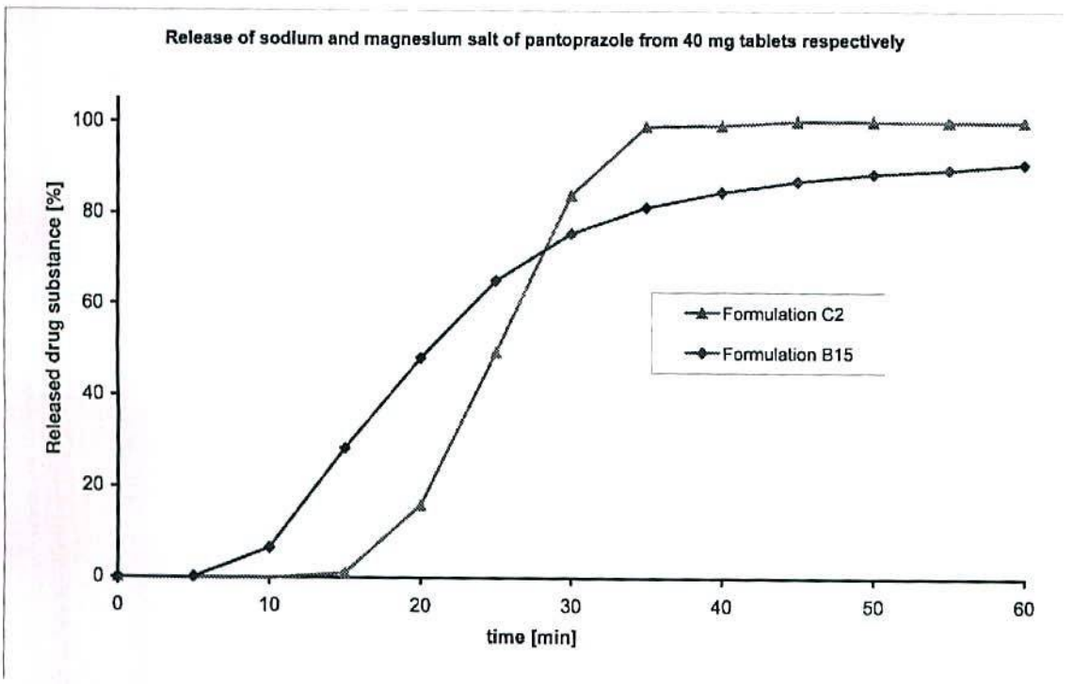

Release of sodium and magnesium salt of pantoprazole from 40 mg tablets respectively
Released drug substance [%]
100
80
60
40
20
0
0
10
20
30
40
50
60
time [min]
Formulation C2
Formulation B15

Figure 2

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under Rule 62a and/or 63 of the European Patent Convention. This report shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number
EP 10 17 5417

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INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC so that only a partial search (R.62a, 63) has been carried out.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
Munich	14 March 2011	Giménez Miralles, J

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X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

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EPO FORM 1503 03.82 (P04E07)

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Application Number
EP 10 17 5417

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EPO FORM 1503 03.82 (P04C10) 2

Europäisches Patentamt
European Patent Office
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INCOMPLETE SEARCH
SHEET C

Application Number
EP 10 17 5417

Claim(s) completely searchable:
3

Claim(s) searched incompletely:
1, 12

Reason for the limitation of the search:

Present independent claim 1 relates to an extremely large number of possible solid dosage forms of pantoprazole magnesium dihydrate. Support within the meaning of Article 84 EPC and/or sufficient disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of those dosage forms claimed, namely those having the structure defined in claim 3 (pellet or tablet core; inert water-soluble intermediate layer; outer enteric coating), wherein the core comprises as binder low MW PVP and/or HPMC.
In the present case, the claims so lack support, and/or the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the dosage forms as disclosed in claims 1 and 3 taken in combination, according to the description and the examples, as indicated by the applicant with his reply to the invitation pursuant to R.63(1) EPC dated 28.02.2011.

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US005385739A

United States Patent [19]

Debregeas et al.

[11] Patent Number: 5,385,739

[45] Date of Patent: Jan. 31, 1995

[54] **STABLE COMPOSITIONS OF GASTROPROTECTED OMERPRAZOLE MICROGRANULES AND PROCESS FOR THE PRODUCTION THEREOF**

[75] Inventors: **Patrice Debregeas**, Versailles; **Gérard Leduc**, Malesherbes, both of France

[73] Assignee: **Ethypharm**, Madrid, Spain

[21] Appl. No.: **78,548**

[22] Filed: **Jun. 16, 1993**

[30] **Foreign Application Priority Data**

Jun. 16, 1992 [FR] France 92 07249

[51] **Int. Cl.**[6] **A61K 9/54**; A61K 9/62

[52] **U.S. Cl.** **424/494**; 424/458; 424/461; 424/462; 424/490; 424/493; 424/497

[58] **Field of Search** 424/461, 462, 493, 494, 424/497

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[57] **ABSTRACT**

The present invention relates to a stable formulation of omeprazole microgranules containing a neutral core consisting of sugar and starch, characterized in that it contains an active layer consisting of a dilution of omeprazole in mannitol in substantially equal amounts. It also relates to a process for producing such formulations.

8 Claims, No Drawings

STABLE COMPOSITIONS OF GASTROPROTECTED OMERPRAZOLE MICROGRANULES AND PROCESS FOR THE PRODUCTION THEREOF

The present invention relates to a pharmaceutical formulation of omeprazole in the form of gastroprotected microgranules having a stability over time compatible with pharmaceutical requirements and to the process for the manufacture of the said microgranules.

Omeprazole, or 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole, an anti-ulcerative substance which reduces gastrointestinal acid secretion, is well known and has been described especially in Swedish Patent No. 78 04231 (Aktiebolaget Hässle Fack).

It is also known that omeprazole has a very low solubility in water but that it is, in contrast, very soluble in alkaline solutions and that it degrades very quickly in acidic medium. Its degradation half-life is ten minutes in aqueous solutions with a pH of less than 4, eighteen hours for a pH equal to 6.5 and approximately 300 days for a pH of 11.

When omeprazole is used orally, it is consequently indispensable to gastroprotect the pharmaceutical form of the active material (gelatin capsules, tablets or powder) so as to prevent any contact of the latter in acidic medium in the stomach while achieving rapid dissolution in the intestinal medium, where the omeprazole must be absorbed, that is to say as soon as ambient pH becomes greater than 6.8.

The in vitro dissolution characteristics of an oral omeprazole formulation as well as the bioavailability results achieved in man with the aid of these oral formulations, consisting of protected granules, have been described in the Scandinavian Journal of Gastroenterology (1985; 20 (suppl. 108): 113–120, Pilbran A., Cederberg C.).

However, it was observed that the conventional enteric granules did not have a sufficient stability over time to be used in a satisfactory pharmaceutical form (gelatin capsules or tablets of microgranules) since degradation of the active principle is rapidly observed when they are placed under usual conditions of use (room temperature of 25° C., degree of humidity between 40 and 75%) with the appearance of harmful degradation products, such as described, for example, in Acta Chemica Scandinavia, 43 (1989), 536–548 (Arne Brändstrom et al.).

In order to overcome these disadvantages, it has especially been proposed (EP-A-0,247,983, Hässle A-G) to mix a suitable amount of omeprazole and of an alkaline sodium, potassium, magnesium or calcium salt or alkaline ammonium salts in a mass of cellulose coating derivatives and of disintegrating agents, so as to produce, by extrusion, a core whose composition is buffered and has an alkaline pH between 7 and 12.

The microgranules thus prepared are then conventionally gastroprotected and correspond to the dissolution and gastroresistance standards defined for an optimum use of the product orally, that is to say a dissolution greater than 75% after 30 minutes in an aqueous medium with a pH equal to 6.8 and a gastroresistance greater than 85% after 2 hours in a medium with a pH equal to 1.2.

Nevertheless, this type of preparation has a number of significant disadvantages, both from the technical and from the economic viewpoint. First of all, it is necessary to prepare combinations of products and mixtures, with risks of overall toxicity and of instability during the manufacturing process. Additionally, it is necessary to use a type of specific and expensive apparatus which adds to the high cost of the active principle and tends to increase the price of the finished product too much for large-scale worldwide use, the daily cost of treatment linked to the use of such a product being much more significant than that obtained by using a treatment of the type involving a bismuth salt and metronidazole or macrolide acting as an anti-acid and agents which destroy *Helicobacter pylori* (agent responsible for the majority of gastrointestinal ulcerations).

The subject of the invention overcomes these disadvantages. It relates to a new stable formulation of gastroprotected omeprazole microgranules and to the process which makes it possible to produce them under advantageous economic conditions.

According to the invention, omeprazole is used in the powder form diluted in a substantially equal amount of mannitol so as to produce a homogeneous and stable suspension and so as to provide better uniformity of the omeprazole content during application on neutral grains consisting of a mixture of sugar and of starch.

The present invention thus relates to a stable formulation of omeprazole microgranules, characterized in that they contain a neutral core consisting of sugar and of starch coated with an active layer comprising a dilution of omeprazole in mannitol in substantially equal amounts.

Dilute powder is understood to mean, according to the invention, a mixture of an omeprazole powder, of a mannitol powder, of sodium lauryl sulfate and of carboxymethylstarch.

Preferentially, the mixed powders have a substantially equal particle size of less than 100 microns.

Substantially equal amounts is understood to mean an omeprazole powder/mannitol powder ratio by weight in the region of 1, that is to say between 0.9 and 1.2.

The neutral cores consisting of sugar and of starch in proportions by weight in the region of 4 parts per 1 part of omeprazole powder have a mean diameter between 0.7 mm and 0.9 mm.

The layer of active principle, or active layer applied to the neutral grains, will preferably have a thickness between approximately 100 and 300 μm (0.1 and 0.3 mm).

To ensure good stability of the active principle during storage of the microgranules according to the invention, the moisture level of the active layer is less than 1%, preferably less than 0.5%.

Additionally, the microgranule according to the invention advantageously comprises an additional protective layer of the active layer consisting of mannitol and of a binding agent, in order to definitively isolate the core, on which the omeprazole is applied, from the external coating layer intended to provide gastroprotection of the active cores.

Preferentially, the binding agent is hydroxypropyl methylcellulose (HPMC) whereas the gastroresistant layer comprises hydroxypropyl methylcellulose phthalate (HPMCP) or anionic copolymers of methacrylic acid and talc.

In order to satisfy the in vitro dissolution criteria of the omeprazole microgranules, according to which at

least 75% of the omeprazole must be dissolved after 30 minutes when the microgranules are placed in an aqueous medium with a pH equal to 6.8 and at a temperature of 37° C., the initial mixture of omeprazole and of mannitol is treated with approximately 10% of carboxymethylstarch (Explotab ®, marketed by the company Mendell), in order to produce complete disintegration of the granules at a pH equal to 6.8, and with approximately 5% of a surface-active agent, such as sodium lauryl sulfate, which improves solubilization of omeprazole in the intestinal medium.

Moreover, solutions, having a high viscosity of the order of 15 centipoises (15×10^{-3} Pa.s), of hydroxypropyl methylcellulose (HPMC) (Pharmacoat ®, marketed by the company Shin-Etsu), used in solution in a mixture of at least 80% ethanol and at most 20% water, for example a mixture of 10 parts of water per 90 parts of 95° ethanol, and in small amounts in order to limit as far as possible the solvent and water content of the granules throughout the manufacture of the active granules, are used as binding solutions for applying the active layer to the neutral grains and then the additional mannitol protection.

Finally, according to an embodiment of the stable omeprazole granules according to the invention, the gastroresistant coating of the microgranules, consisting of hydroxypropyl methylcellulose phthalate (HPMCP) (HP 50 R, marketed by the Company Shin-Etsu) in 7.5% solution in an 80/20 mixture by mass of acetone and 95° ethanol, is applied in external layers after pretreatment of the active omeprazole and mannitol granules by spraying with a 33% sucrose syrup, in a 44/56 by mass water/ethanol mixture, this sugar syrup having a total sucrose weight of approximately 25% with respect to the amount of final gastroresistant coating. This external layer may contain talc as a lubricating agent.

Throughout all the various application and coating stages, the temperature of the granules is maintained between 32° C. and 38° C. and, between each stage, a drying is carried out so that the solvents and water contents are minimal, the final content being less than 1% for water and 2000 ppm for ethanol.

Other characteristics and advantages of the invention will become apparent in the light of the following examples.

EXAMPLE 1

Process for the preparation of micro granules containing 8.41% of omeprazole by weight

All the amounts mentioned are expressed in kg of dry mass for a final amount equal to 237.80 kg of microgranules having an omeprazole content of 84.1 mg per gram of microgranules.

COMPOSITION	
Neutral sugar and starch grains	80.00
Active layer:	
Omeprazole	20.00
Mannitol	20.00
Carboxymethylstarch (CMS)	4.00
Sodium lauryl sulfate	2.00
Additional protective layer:	
Mannitol	50.00
Sucrose	8.00
HPMC, 15 centipoises	3.20
Gastroresistant layer	
HPMCP	32.00
Talc	18.60

-continued

COMPOSITION	
	237.80

The process, according to the invention, consists in preparing a dilution of 20 kg of omeprazole in 20 kg of mannitol in the presence of 4 kg of CMS and of 2 kg of sodium lauryl sulfate, and then binding this dry dilution onto 80 kg of neutral sugar and starch grains, whose diameter is between 0.7 and 0.9 mm, with the aid of a 4% solution of HPMC (1.6 kg) in water (20 parts) and 95° ethanol (80 parts) in a circular turbine with an inclined flat bottom, and then protecting the active grains thus obtained with the aid of 50 kg of mannitol applied with the rest of the HPMC solution (i.e. 1.6 kg), and then pretreating the granules thus protected with a 33% sugar syrup (8 kg of sucrose) consisting of 44 parts of water per 56 parts of 95° ethanol and in finally applying the gastroprotection coating at a charge of 32 kg of HPMCP in 7.5% solution in a mixture of 80 parts of 95° ethanol per 20 parts of acetone.

The granules thus obtained show a gastroresistance of greater than 85% in a medium with a pH of 1.2, since, after 2 hours at 37° C., the amount of unreleased omeprazole in this medium is 91.7%. In an aqueous medium with a pH equal to 6.8, the dissolution of the granules shows, after 30 minutes, an omeprazole degree of 92%, i.e. an amount greater than 75% which is the minimum acceptable standard.

At the end of 12 and 24 months, the respective gastroresistance values are 92.1% and 92.8% and the dissolutions at a pH of 6.8 are 91.4% and 93.8% under the same operating conditions.

Moreover, the very-pale beige color of the microgranules stored in gelatin capsules at room temperature and an external humidity of 60% in glass bottles fitted with protective caps and containing desiccating capsules is maintained constant for a period of at least 24 months.

EXAMPLE 2

Stability Tests

The testing of the stability of omeprazole was carried out on 4 batches of gelatin capsules comprising microgranules according to the invention and one batch of microgranules. The monitored batches, the storage conditions, the methods of analyses and the results are presented below.

1. MONITORED BATCHES

Omeprazole gelatin capsules
C458-1-2, C458-1-6, C458-2-3 and C458-2-4
Omeprazole microgranules
UQM 001-3

BATCHES	DATES OF MANUFACTURE	STORAGE TIME (months)
C458-1-2	June 1983	36
C458-1-6	February 1984	36
C458-2-3	September 1984	24
C458-2-4	October 1984	24
UQM 001-3	October 1990	3

2. STORAGE CONDITIONS

25° C.-60% Relative humidity
30° C.-30–40%, 60% Relative humidity
37° C.-20–30%, 90% Relative humidity

50° C.-80% Relative humidity
Refrigerator

3. ANALYSIS OF THE SAMPLES

a. gelatin capsules

Sample solution

A - For the quantitative determination of omeprazole, introduce the contents of 5 gelatin capsules into a 250 ml volumetric flask, then introduce 200 ml of methanol-/aqueous ammonia (95/5) solution and stir magnetically for 30 minutes. Complete to volume using the same solvent. Filter and dilute 10 ml of the filtrate in a 100 ml volumetric flask with 30 ml of dichloromethane and complete to volume using a methanol/aqueous ammonia/dichloromethane (24/1/75) solution.

B - To determine the degradation products, dissolve the contents of 2 gelatin capsules in 8 ml of the methanol/aqueous ammonia (95/5) solution, with magnetic stirring for 30 minutes. Filter and dilute 2.5 ml of the filtrate to 100 ml in dichloromethane. Inject immediately.

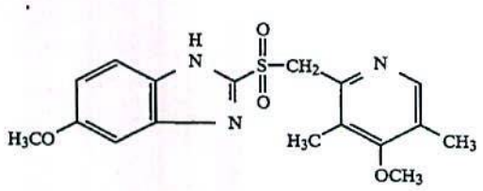
Equipment and conditions

HPLC apparatus equipped with a U.V. detector.
7 μm silica precolumn with a length of 15 mm and an internal diameter of 3.2 mm (Brownlee or equivalent).
5 μm Lichrosorb Si 60 column, with a length of 124 mm and an internal diameter of 4 mm (Hibar Merck or equivalent).
Flow rate: 1 ml/min.
Reading at 280 nm
Injection: 40 μl.

Monitoring of the system

Once stability of the baseline has been obtained, the system is monitored in the following way:

Dissolve 5 mg of omeprazole standard and 5 mg of the corresponding sulfone H 168/66 (whose formula is reproduced below) in 100 ml of the mobile phase. Inject 40 μl several times until a constant retention time is obtained (difference between two injections <1%).



The retention time of omeprazole is 10 minutes and that of the sulfone H 168/66 is 8 minutes.

b. microgranules

Determination of the omeprazole content of the microgranules

The omeprazole content of the microgranules is determined by ultraviolet spectrophotometry after separation by high performance liquid chromatography.

Reagents

Acetonitrile for HPLC (for example Carlo Erba ref. 412409)
Dibasic sodium phosphate (Na_2HPO_4)
Monobasic sodium phosphate ($NaH_2PO_4.H_2O$)
Distilled water
Reference substance: omeprazole

Equipment

Apparatus for liquid chromatography with a UV detector (280 nm):
2 stainless steel columns in series:
precolumn: length 1.5 cm - internal Ø3.2 mm - particle size 7 μm
column: length 12.5 cm - internal Ø4 mm - particle size 5 μm
Stationary phase: Lichrosorb RP 18
Injection system: for 20 μl amounts (for example Wisp 712 automatic injector).
Integrator: Perkin Elmer LCI 100 or Waters 645 Data Module

Gastroresistance and dissolution tests

The microgranules are stirred for 2 h 30 in suitable media at constant temperature (37° C.±0.5° C.) in a dissolution apparatus.

Equipment

The dissolution apparatus used is the paddle apparatus described in the European Pharmacopeia.
Speed used: 500 ml of medium with a pH of 1.2. Addition of 400 ml of medium with a pH of 7.6.

Media

Medium I: Medium having acid strength:

Introduce 2 grams of sodium chloride and 7 ml of concentrated (37%) hydrochloric acid into a 1 liter volumetric flask. Complete to volume using purified water. Stir until dissolved. The pH of this solution should be 1.2±0.05.

Medium II: Medium with a pH of 7.6 (addition)

0.235M Dibasic sodium phosphate solution (Na_2HPO_4). Prepare 1 liter of solution for 2 vessels.

4. RESULTS AND CONCLUSIONS

The results are summarized in the tables below.

During determination of the impurities content, two main impurities are detected in all the batches. In the tables of results, they are identified by the designations I and I'.

A: Storage period (months)
B: Storage conditions - °C. - Relative humidity
C: Appearance
D: Disintegration (min)
E: Omeprazole assay (mg/gel)

Omeprazole gelatin capsules, batch C458-1-2

A	B		C	D	E	F I %	F I' %	F Others %
0			a	6	20.3	<0.5	<0.5	<0.2
6	25	60	a	5	20.6	<0.5	<0.5	<0.2
	30	60	a	7	20.1	<0.5	<0.5	<0.2
	50	80	c	7	19.4	<0.5	<0.5	<0.3
12	25	60	a	5	20.5	<0.5	<0.5	<0.2
	30	60	b	6	20.5	<0.5	<0.5	<0.2
18	25	60	a	6	19.8	<0.5	<0.5	<0.2
	30	60	b	6	20.1	<0.5	<0.5	<0.2
24	25	60	a	6	20.7	<0.5	<0.5	<0.2
	30	60	c	7	20.2	<0.5	<0.5	<0.3
30	25	60	a	6	20.3	<0.5	<0.5	<0.3
36	25	60	b	6	19.9	<0.5	<0.5	<0.3
refrigerator			a	6	20.8	<0.5	<0.5	<0.2

a = white,
b = colored, conforms,
c = colored, does not conform

Omeprazole gelatin capsules, batch C458-1-6

A	B		C	D	E	F I %	F I' %	F Others %
0			a	5	19.4	<0.5	<0.5	<0.2
6	25	60	a	5	19.6	<0.5	<0.5	<0.2
	30	60	a	6	19.5	<0.5	<0.5	<0.2
	50	80	c	7	18.7	<0.5	<0.5	<0.4

-continued

Omeprazole gelatin capsules, batch C458-1-6

A		B	C	D	E	F I %	F I' %	F Others %
12	25	60	a	5	19.2	<0.5	<0.5	<0.2
	30	60	b	6	19.3	<0.5	<0.5	<0.2
18	25	60	a	5	19.7	<0.5	<0.5	<0.2
	30	60	b	5	19.1	<0.5	<0.5	<0.3
24	25	60	a	6	19.0	<0.5	<0.5	<0.2
	30	60	c	6	19.2	<0.5	<0.5	<0.3
30	refrigerator		a	6	19.8	<0.5	<0.5	<0.2
	25	60	a	5	19.3	<0.5	<0.5	<0.2
36	refrigerator		a	6	19.8	<0.5	<0.5	<0.2
	25	60	b	5	19.2	<0.5	<0.5	<0.2

a = white,
b = colored, conforms,
c = colored, does not conform

Omeprazole gelatin capsules, batch C458-2-3

A		B	C	D	E	F I %	F I' %	F Others %
0			a	<5	21.2	<0.5	<0.5	<0.2
6	refrigerator		a	<5	20.9	<0.5	<0.5	<0.2
	25	60	a	5	21.1	<0.5	<0.5	<0.2
12	refrigerator		a	5	20.8	<0.5	<0.5	<0.2
	25	60	a	<5	20.7	<0.5	<0.5	<0.2
18	refrigerator		a	<5	20.6	<0.5	<0.5	<0.2
	25	60	a	5	20.4	<0.5	<0.5	<0.2
24	25	60	a	6	20.7	<0.5	<0.5	<0.2

a = white,
b = colored, conforms,
c = colored, does not conform

Omeprazole gelatin capsules, batch C458-2-4

A		B	C	D	E	F I %	F I' %	F Others %
0				6	20.7	<0.5	<0.5	<0.2
6	25	60	a	<5	20.8	<0.5	<0.5	<0.2
12	25	60	a	5	20.3	<0.5	<0.5	<0.2
18	25	60	a	6	20.5	<0.5	<0.5	<0.2
24	refrigerator		a	5	20.0	<0.5	<0.5	<0.2
	25	60	b	5	20.4	<0.5	<0.5	<0.5

a = white,
b = colored, conforms,
c = colored, does not conform

Omeprazole microgranules, UQM 001-3

A: Storage period (months)
B: Storage conditions - °C. - Relative humidity
C: Appearance
D: Omeprazole assay (mg/g)
E: Gastroresistance test
F: Dissolution test - %

A	B		C	D	E	F
0			a	78.0	95.9	95.0
1	25	55–65	a	80.8	93.9	94.0
	30	30–40	a	81.2	94.4	95.0
	37	20–40	a	80.4	97.0	97.0
	37	90	a	77.6	97.5	100.0
3	25	56–65	a	81.4	91.6	92.0
	30	30–40	a	79.1	95.7	96.0
	37	20–40	a	80.2	92.0	93.0
	37	90	c	41.9	—	—

a = white,
b = colored, conforms,
c = colored, does not conform

The gelatin capsules have good stability in the refrigerator and at 25° C., for up to 36 months of storage. All the impurities have a concentration of less than 0.50%.

The impurities content increases a little more with temperature and humidity, and can be sufficient to cause coloration of the granules.

The microgranules stored in bulk have good stability for 3 months at room temperature and 55–65% relative humidity, at 30° C. and 30–40% relative humidity and at 37° C. and 20–30% relative humidity, and for month at 37° C. and 90% relative humidity.

TERM OF VALIDITY

In the light of the results obtained, the specialty is stable for 36 months provided that it does not exceed 25° C. during this period.

SPECIFICATIONS	
1. Appearance	hard gelatin capsules containing off-white to more or less dark-beige granules without foreign particles.
2. Mean weight	approximately 235 mg ± 10%
3. Omeprazole content	18.0–22.0 mg/gelatin capsule (90–110%)
4. Resistance in acid medium	≧85%
5. Release at a pH of 6.8	≧75%
6. Degradation products	total content ≦2.0% individual contents ≦0.5%

Of course, a person skilled in the art will be able to introduce variants into the embodiments of the microgranules according to the invention, in particular by using coating apparatuses such as fluidized beds in place of the flat-bottomed turbines described above, or also by using methacrylic polymers as gastroprotection materials (for example Eudragit ® L 100-55 or L 30 D of the company Rohm & Hass) or other gastroresistant polymers, without departing from the context and scope of the invention.

On the other hand, the invention is not intended to produce microgranules by the conventional extrusion techniques already described in the prior art, these techniques requiring the use of omeprazole in solution in a mass containing solvents and water, which are avoided by virtue of the embodiments of the process described above in order to overcome the consequences of the instability of omeprazole under such conditions.

We claim:

1. A stable formulation of omeprazole microgranules containing a neutral core of sugar and starch and an active layer consisting of a dilution of omeprazole in mannitol in substantially equal amounts, wherein the active omeprazole layer contains about 10% by weight of carboxymethylstarch, about 5% by weight of a sodium lauryl sulfate surface-active compound, and wherein the dilution of omeprazole in mannitol is applied to the neutral core by means of hydroxypropyl methylcellulose as a high viscosity binder.

2. The formulation as claimed in claim 1, wherein the formulation contains, at the surface of the active omeprazole layer, an additional protective layer consisting of mannitol.

3. The formulation as claimed in claim 2, wherein said protective layer is applied by means of a high viscosity binder of hydroxypropyl methylcellulose.

4. The formulation as claimed in claim 1, wherein the active grains contain an external gastroprotection layer

consisting of a gastroresistant coating of hydroxypropyl methylcellulose phthalate and talc.

5. A process for producing the formulations as claimed in claim 1, wherein a dry dilution of mannitol and of omeprazole is applied to neutral grains consisting of sugar and of starch with the aid of a high-viscosity binding solution of hydroxypropyl methylcellulose in solution in a mixture of at least 80% ethanol and at most 20% water.

6. The process as claimed in claim 5, wherein each application of the dry dilution is followed by drying at a temperature between 35° C. and 40° C. for a time which makes it possible to lower the water content of the active microgranules to 1% and their ethanol content to 2000 ppm.

7. The process as claimed in claim 5, wherein neutral microgranules are used whose size is between 0.7 and 0.9 mm.

8. The process as claimed in claim 5, wherein flat-bottomed turbines are used to carry out the active dilution applications and the gastroprotection coatings.

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US005540945A

United States Patent [19]

Ikushima

[11] Patent Number: 5,540,945

[45] Date of Patent: Jul. 30, 1996

[54] **PHARMACEUTICAL PREPARATIONS FOR ORAL ADMINISTRATION THAT ARE ADAPTED TO RELEASE THE DRUG AT APPROPRIATE SITES IN THE INTESTINES**

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[21] Appl. No.: **366,400**

[22] Filed: **Dec. 29, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 2,099, Jan. 8, 1993, abandoned, which is a continuation of Ser. No. 640,425, filed as PCT/JP90/00596, May. 10, 1990, abandoned.

[30] **Foreign Application Priority Data**

May 11, 1989 [JP] Japan 1-116086

[51] **Int. Cl.**[6] **A61K 9/16**; A61K 9/54

[52] **U.S. Cl.** **424/490**; 424/489; 424/493; 424/494; 424/496; 424/497; 424/458; 424/459; 424/461; 424/462

[58] **Field of Search** 424/458, 459, 424/461, 462, 468, 470, 471, 472, 474, 493, 494, 495, 497, 489–492

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Attorney, Agent, or Firm—Marshall, O'Toole, Gerstein, Murray & Borun

[57] **ABSTRACT**

The improved pharmaceutical preparation for oral administration which is adapted to release the drug at appropriate sites in the intestines comprises: a core that comprises an active ingredient and a pharmaceutically acceptable excipient, a first layer that covers the core and which comprises an enteric or water-soluble ingredient and an optional insoluble ingredient, a second layer that covers the first layer and which comprises a non-enteric ingredient that dissolves upon reacting with at least one ingredient in the core, and a third layer that covers the second layer and which comprises an enteric ingredient. This preparation is characterized in that it will not release the active ingredient until after it reaches a desired site in the intestines and that, in addition, it is capable of controlling the rate at which the active ingredient is released after it has reached the desired site. Therefore, this preparation is particularly effective in administering active ingredients having absorption specificity at specific sites in the intestines or for treating diseases at specific sites in the intestines.

2 Claims, 5 Drawing Sheets

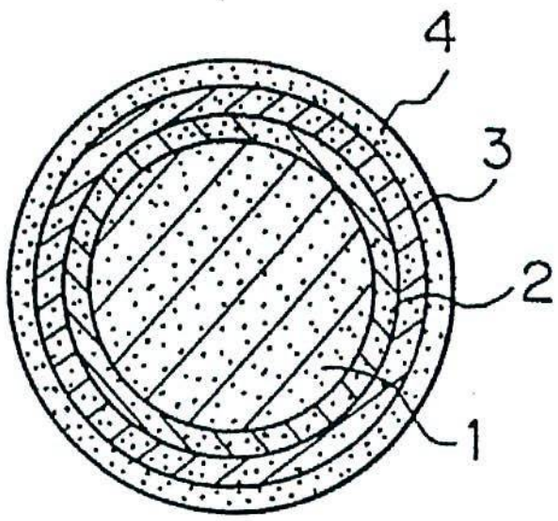


Fig. 1

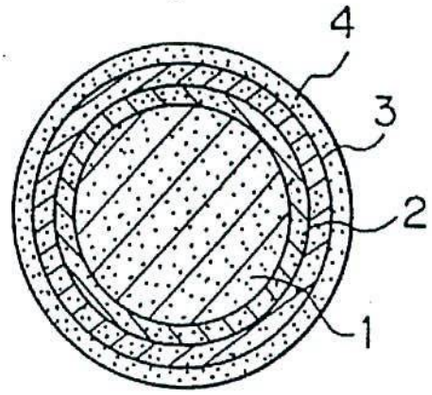
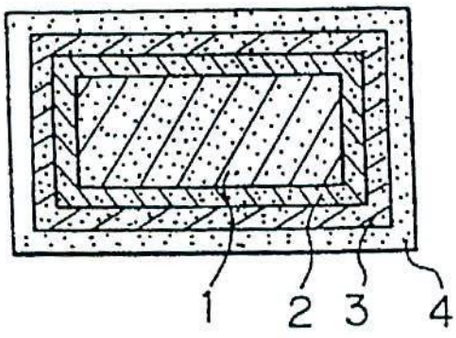


Fig. 2



54

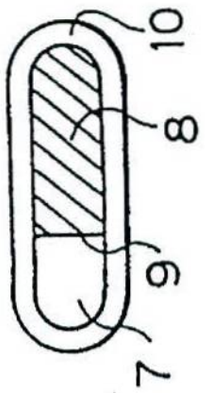


Fig. 3E

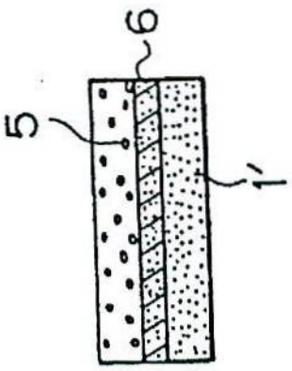


Fig. 3C

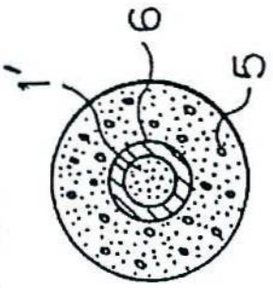


Fig. 3D

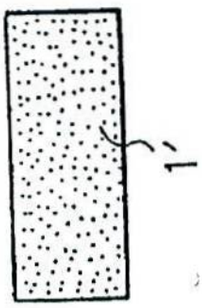


Fig. 3A

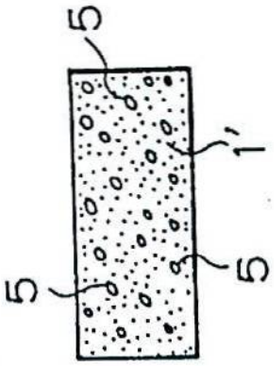


Fig. 3B

Fig. 4

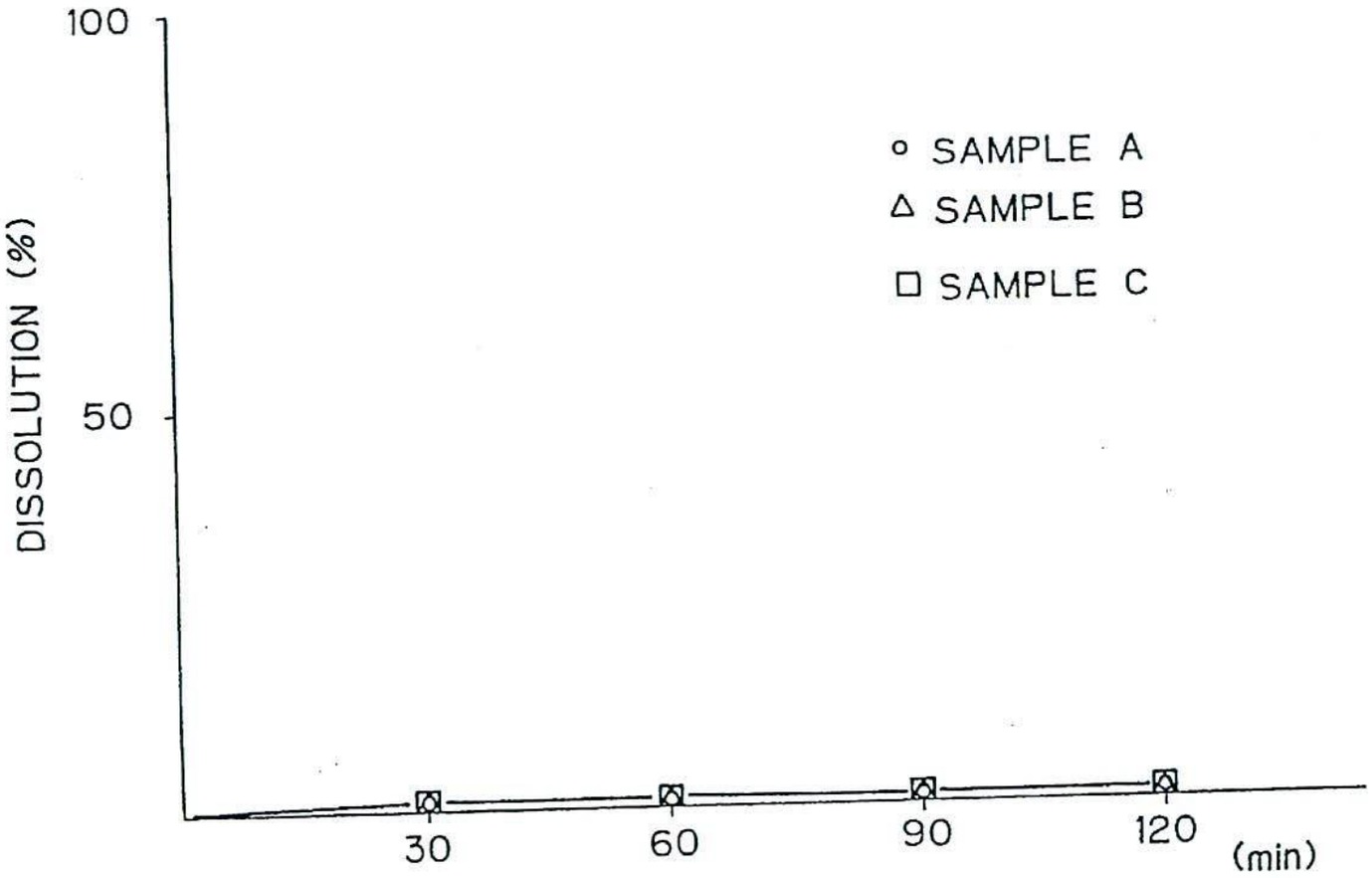
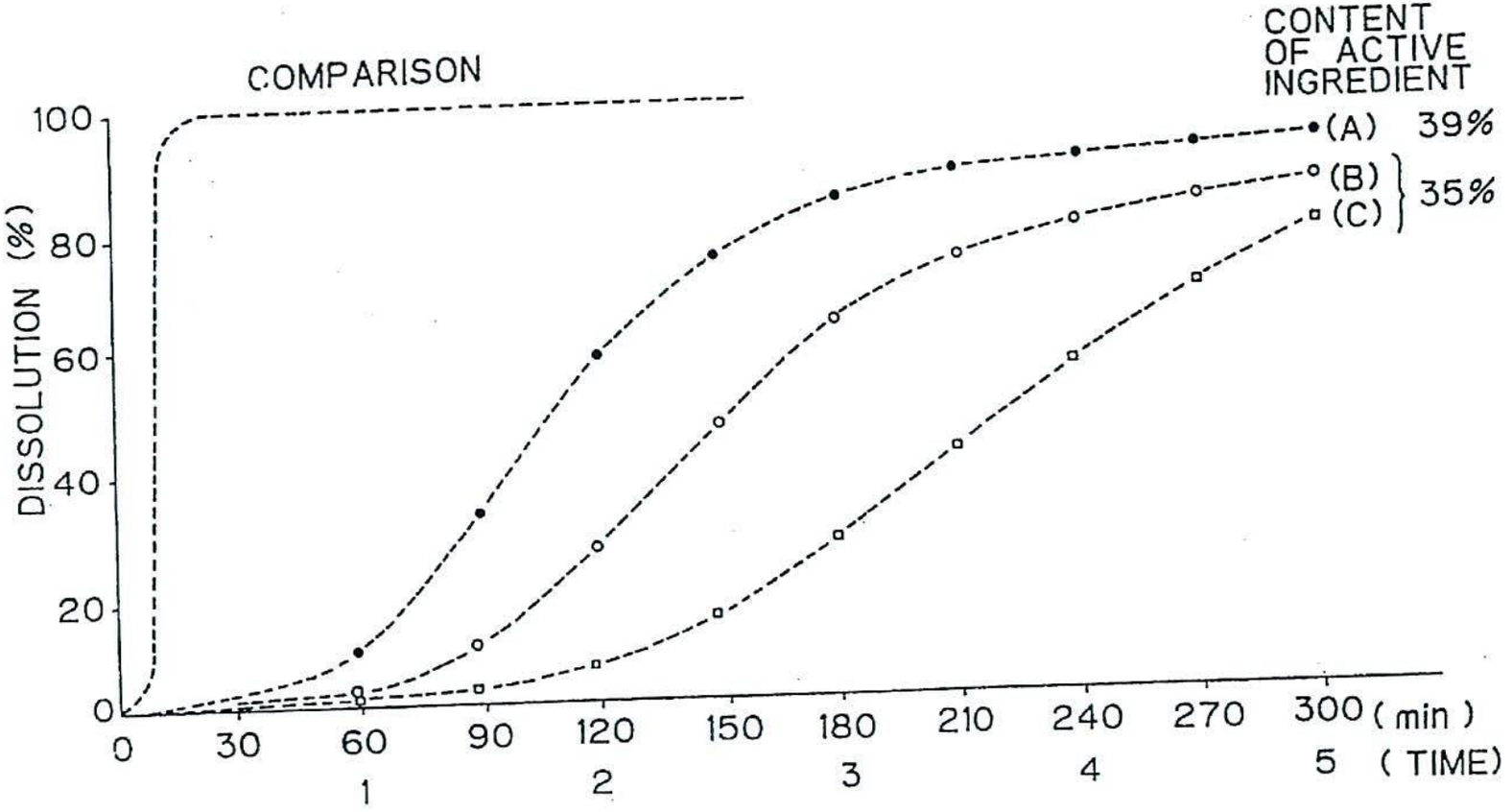
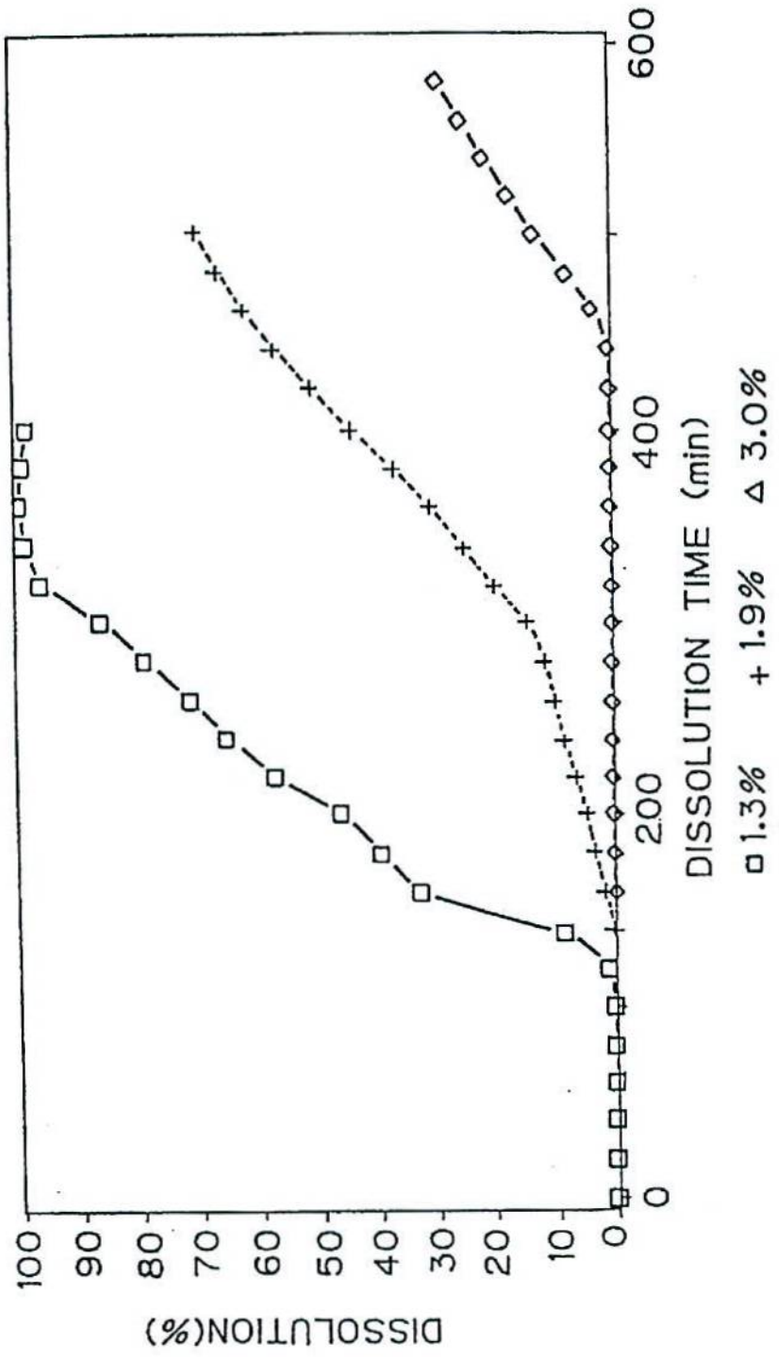


Fig. 5


CONTENT OF ACTIVE INGREDIENT
COMPARISON
(A) 39%
(B)
(C)
35%
DISSOLUTION (%)
100
80
60
40
20
0
0
30
60
90
120
150
180
210
240
270
300
(min)
1
2
3
4
5
(TIME)

57

Fig. 6


DISSOLUTION(%)
100
90
80
70
60
50
40
30
20
10
0
0
200
400
600
DISSOLUTION TIME (min)
□ 1.3% + 1.9% Δ 3.0%

PHARMACEUTICAL PREPARATIONS FOR ORAL ADMINISTRATION THAT ARE ADAPTED TO RELEASE THE DRUG AT APPROPRIATE SITES IN THE INTESTINES

This is a Continuation of U.S. application Ser. No. 08/022, 099 filed on Jan. 8, 1993, now abandoned which is a continuation of U.S. application Ser. No. 07/640,425, filed as PCT/JP90/00596, May 10, 1990, now abandoned.

TECHNICAL FIELD

This invention relates to pharmaceutical preparations for oral administration that are adapted to release the drug at appropriate sites in the intestines. More particularly, this invention relates to the structure of a pharmaceutical preparation for oral administration that enables the drug to be released continuously at specific sites in the intestines.

BACKGROUND ART

Pharmaceutical preparations for oral administration are generally intended to have the drug disintegrated in the stomach, etc. to insure that its efficacy is exhibited as quickly as possible. Thus, little R&D efforts have so far been directed to pharmaceutical preparations for oral administration that are so adapted as to release the drug only at specific sites in the intestines. Even if L-ascorbic acid containing preparations are administered orally with a view to delivering the drug to the large intestine so that it is released there, the drug is decomposed in the stomach and mostly absorbed by the small intestine, with little being delivered to the large intestine.

Sustained-release preparations have been developed as pharmaceuticals that are administered once or twice a day and which yet are capable of maintaining the blood concentration of the drug beyond a certain level over a prolonged time. However, even such sustained-release preparations are incapable of permitting the drug to be released only at desired sites in the intestines. For instance, even if it is intended to have the drug absorbed by the large intestine, part of the drug will be released before it reaches the large intestine since it takes 4–5 hours for the administered drug to reach the large intestine during a fasting period. Further, the drug reaching the large intestine is released only slowly so that the percent absorption of the drug is too low to insure efficient administration of the drug. Besides sustained-release preparations, administration can be made through the rectum either in the form of suppositories or by means of enema but even these methods are incapable of delivering the drug effectively to every part of the large intestine. Hence, heretofore, no means have been available by which salazosulfapyridine and prednisolone which are therapeutics for ulcerous colitis can be efficiently administered to reach appropriate sites in the large intestine.

DISCLOSURE OF THE INVENTION

Under these circumstances, the present inventors conducted intensive studies in order to develop a pharmaceutical preparation for oral administration that would not release the drug until after it reached a desired site in the intestines and which, after reaching the desired site, would release all the drug within a desired period of time. As a result of these studies, the present invention has been accomplished.

The pharmaceutical preparation of the present invention which is to be administered orally and which is adapted to release the drug at appropriate sites in the intestines comprises:

(a) a core that comprises an active ingredient and a pharmaceutically acceptable excipient;

(b) a first layer that covers the core and which comprises an enteric ingredient;

(c) a second layer that covers the first layer and which comprises a non-enteric ingredient that dissolves upon reacting with at least one ingredient in the core; and

(d) a third layer that covers the second layer and which comprises an enteric ingredient.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows an example of the structure of a granule according to the present invention;

FIG. **2** shows an example of the structure of a tablet according to the present invention;

FIG. **3** shows various types (A to E) of the core in the pharmaceutical preparation of the present invention; and

FIGS. **4**, **5** and **6** are each a graph showing the results of a dissolution test in terms of the relationship between dissolution time and percent dissolution.

BEST MODE FOR CARRYING OUT THE INVENTION

The core of the pharmaceutical preparation of the present invention comprises an active ingredient and an excipient. The active ingredient can be selected from a broad range of efficacious substances that can be absorbed by the intestines and/or can be adhered to the intestinal walls, etc. Particularly, substances that are efficiently absorbed at a specific site such as the large intestine as well as therapeutics for diseases in the intestines can be used effectively.

The core may contain a disintegrator that accelerates the release of the active ingredient.

The core may further contain an additive material that dissolves the second layer. Such additive materials are not always necessary if the active ingredient dissolves the second layer. However, if the active ingredient has little or no dissolving power or if sufficient dissolving action cannot be exhibited even though the active ingredient has a strong dissolving power because it is present in a very small amount, additive materials will be used effectively. Additive materials are selected as appropriate in accordance with the component of the second layer. For instance, if a substance that is disintegratable in the stomach is used in the second layer, with a non-acidic substance such as indomethacin being used as the active ingredient, water-soluble acidic materials such as organic acids can be used as additive materials.

The third layer which forms the outermost shell of the pharmaceutical preparation of the present invention comprises an enteric substance. The third layer must be such that it prevents the inner layers from being destroyed in the stomach after the preparation is administered orally while it dissolves only after the preparation gets into the intestines. Hence, it is required that the third layer not decompose with gastric juice but can be dissolved with intestinal juice. Specific examples of materials that can be used to make the third layer include: synthetic high-molecular weight compounds such as cellulose acetate phthalate (CAP), cellulose propionate phthalate, cellulose acetate maleate, polyvinyl

alcohol phthalate, styrene-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate (HPMCP), hydroxypropylmethyl cellulose acetate succinate (HPMCAS), methacrylic acid/methyl methacrylate copolymer, ethyl methacrylate-methyl methacrylate-chloro-trimethylammonium ethyl methacrylate copolymer, as well as those substances which can be used as enteric coating agents, as exemplified by the enteric ingredients listed below in connection with the description of the first layer.

The second layer comprises a non-enteric ingredient that dissolves upon reacting with at least one ingredient in the core. The second layer is provided in order to start the release of the active ingredient at a predetermined site in the intestines and to control the time over which it is released. The component of the second layer must be a non-enteric one that dissolves upon reaction with at least one ingredient in the core. Specific examples of such components include polyvinyl acetate diethyl aminoacetate (AEA), polyvinyl aminoacetal, and dimethylaminoethyl methacrylate-methyl methacrylate copolymer. Among these, substances that dissolve in an acidic region (pH 1–5) but which will not dissolve in a neutral or alkaline region are preferably used.

The first layer comprises an enteric or water-soluble ingredient. The first layer is present in order to insulate the core from the second layer, thereby controlling the time at which the active ingredient starts to be released. Specific examples of the component of the first layer include: enteric ingredients such as hydroxypropylmethyl cellulose phthalate (HPMCP), hydroxypropylmethyl cellulose acetate succinate (HPMCAS), methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methyl methacrylate-chlorotrimethylammonium ethyl methacrylate copolymer, cellulose acetate phthalate (CAP), cellulose propionate phthalate, cellulose acetate maleate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, styrene-acrylic acid copolymer, and methyl acrylate-methacrylic acid copolymer; and water-soluble ingredients such as cellulosic derivatives (e.g. acetyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and carboxymethyl cellulose sodium) and natural high-molecular weight compounds (e.g. gelatin). The release start time can be delayed by adding insoluble ingredients such as ethyl cellulose (E.C). Such insoluble ingredients can be added in amounts ranging from 0 to 50% of the first layer.

Each of the first, second and third layers may have plasticizers, antistats and other compounds incorporated therein for the purpose of improving coating and film-forming properties.

When it enters the intestines, the pharmaceutical preparation of the present invention first has the third layer dissolved by intestinal juice. Since the second layer is non-enteric, intestinal juice will infiltrate the preparation without dissolving the second layer. When the intestinal juice reaches the first layer, infiltration into the first layer or dissolution of this layer itself will start. When the infiltration into or dissolution of the first layer causes the core to contact the solution, the ingredients of the core will diffuse through the solution. Upon contact with the additive material and/or active ingredient in the core, the second layer starts to dissolve, eventually causing the active ingredient to be released into the intestines.

A specific structure of the preparation of the present invention is designed in such a way that the active ingredient can be released at a desired site in the intestines in accordance with the above-described mechanism of release. For example, the time required for intestinal juice to reach the first layer or the time required for dissolution by the additive materials, etc. can be controlled by varying the thickness of the second layer. Further, the release rate of the active ingredient can also be controlled by selecting proper combinations of the additive materials and the second layer which is to be dissolved by them or by changing the component in the second layer. It should be noted here that the second layer is required to have such a strength as to prevent it from being destroyed before it is dissolved by the active ingredient or additive materials.

The individual layers in the preparation of the present invention are usually coated in the following amounts. In the case of granules, the first layer is coated in an amount of 5–60 wt % of the core, the second layer is coated in an amount of 10–80 wt % of the core with the first layer, and the third layer is coated in an amount of 10–30 wt % of the core with the first and second layers. In the case of tablets or capsules, the first, second and third layers are usually coated in the respective amounts of 0.5–10%, 0.5–10% and 1–10%, on the basis of the bore tablet or capsule weight. As already described above, the coating weights of the respective layers can be appropriately selected in order to obtain pharmaceutical preparations for oral administration that are adapted to release the drug at desired sites in the intestines.

The structure of the core is not limited in any particular way as long as it is capable of releasing the active ingredient by the mechanism described above. Specific examples of the core structure are listed below: a structure that solely consists of the active ingredient and an excipient in the absence of any additive material; a structure in which the active ingredient and an additive material are present uniformly (FIG. 3A); a structure in which a predetermined amount of additive material is mixed within the active ingredient (FIG. 3B); a structure having the active ingredient and an additive material present in different layers, a structure having an isolating layer between a layer made of the active ingredient and a layer made of an additive material (FIGS. 3C and 3D); and a structure having the active ingredient placed within a capsule (FIG. 3E). When additive materials are to be used, factors such as their reactivity with the active ingredient have to be taken into account. Particularly in the case where additive materials are acidic whereas the active ingredient is not acidic, the structure shown in FIG. 3B, C, D, or E is preferably employed.

The process for producing the pharmaceutical preparation of the present invention is not limited in any particular way and customary methods known to one skilled in the art can be employed. For example, the core can be coated with various apparatus equipped with conventionally known pan coaters, fluidized coaters and a forced-air drying mechanism. Coating solutions are also not limited in any particular way and various ingredients can be used, such as plasticizers, surfactants, higher alcohols, higher aliphatic acid esters of glycerin for improving the film-forming property, additives for adjusting water permeability, water vapor permeability and light transmission (e.g., stearic acid, polyethylene glycol, talc and titanium oxide), antistats that are added for the purpose of improving the efficiency of coating operations (e.g., stearic acid and polyethylene glycols), silicone resins for defoaming purposes, dyes and inorganic pigments for coloring purposes, and flavoring agents.

The pharmaceutical preparation of the present invention is chiefly characterized in that the active ingredient will not be released until after it reaches a desired site in the intestines and that the release rate of the active ingredient can be controlled after reaching the desired site. Hence, the phar-

maceutical preparation of the present invention can be used with particular effectiveness not only in administering active ingredients that have absorption specificity at specific sites in the intestines such as in the large intestine but also for treating diseases at specific sites in the intestines. This has the potential to allow heretofore impossible or difficult drug administrations and disease treatments to be accomplished effectively. For example, the pharmaceutical preparation of the present invention will prove extremely effective as a means of effective administration of reducing agents for the purpose of preventing not only the occurrence of polyp in the large intestine due to a significantly oxidizing environment but also the development of such polyp into adenoma or cancer.

The following examples are provided for the purpose of further illustrating the present invention in a more specific and detailed manner but it should be understood that the scope of the present invention is only determined by the claims and that it is in no way limited by those examples.

In the following, all "parts" are on a weight basis.

EXAMPLE 1

Granules as a Preparation for Delivering L-Ascorbic Acid to the Large Intestine

L-ascorbic acid (72 parts), crystalline cellulose (15 parts), lactose (5 parts), stearic acid (5 parts) and a 50% ethanol aqueous solution containing 10 wt % hydroxypropyl cellulose were kneaded in such a way that the content of hydroxypropyl cellulose would be equivalent to 3 parts as solids. The mixture was charged into a cylindrical granulator equipped with a 0.8 mm$^{\Phi}$ net, where granulation and drying were effected.

The dry granules obtained (300 parts) were coated in the usual manner using a coating solution consisting of hydroxypropylmethyl cellulose phthalate (HP-55, 7 parts), purified shellac (0.7 parts), acetylated monoglyceride (0.7 parts), methylene chloride (45.8 parts) and ethanol (45.8 parts) in such a way that the solids content would be equivalent to 75 parts, whereby the granules were coated with a first layer.

The granules with the first layer (300 parts) were coated in the usual manner using a coating solution for a second layer that consisted of AEA (5 parts), polyethylene glycol (2 parts), ethanol (40 parts) and methylene chloride (53 parts) in such a way that the solids content would be equivalent to 60 parts, whereby the granules were further coated with a second layer.

The granules with the first and second layers (300 parts) were coated using a coating solution of the same composition as the first layer in such a way that the solids content would be 60 parts, whereby granules were obtained as a preparation for delivering L-ascorbic acid to the large intestine.

EXAMPLE 2

The bare granules (300 parts) prepared in Example 1 were coated in the usual manner using a coating solution consisting of hydroxypropylmethyl cellulose acetate succinate (HPMCAS, 10 parts), triethyl citrate (4 parts) and pure water (86 parts) in such a way that the solids content would be equivalent to 60 parts, whereby the granules were coated with a first layer. Coating of a second and a third layer was accomplished as in Example 1.

EXAMPLE 3

A first layer was applied in the usual manner using a coating solution consisting of hydroxypropylmethyl cellulose acetate succinate (HPMCAS, 10 parts), triethyl citrate (4 parts) and pure water (86 parts) in such a way that the solids content would be equivalent to 90 parts. Subsequently, coating of a second and a third layer was accomplished as in Example 1.

EXAMPLE 4

Granules as a Preparation for Delivering Indomethacin to the Large Intestine

Indomethacin (10 parts), lactose (50 parts), citric acid (20 parts), crystalline cellulose (15 parts) and hydroxypropyl cellulose (5 parts) were mixed and kneaded in the presence of water. The mixture was granulated and dried in a cylindrical granulator equipped with a 0.8 mm$^{\Phi}$ net.

The dry granules (300 parts) obtained were coated with a first, a second and a third layer as in Example 3, whereby a preparation for delivering indomethacin to the large intestine was obtained.

EXAMPLE 5

Granules as a Preparation for Delivering Salazosulfapyridine to the Large Intestine

Salazosulfapyridine (50 parts), low-substitution hydroxypropyl cellulose (10 parts), tartaric acid (20 parts), crystalline cellulose (5 parts), corn starch (10 parts) and hydroxypropyl cellulose (5 parts) were mixed and kneaded in the presence of water. Then, the mixture was granulated and dried in a cylindrical granulator equipped with a 1.0 mm$^{\Phi}$ net.

The dried granules (300 parts) obtained were coated with a first, a second and a third layer as in Example 3, whereby a preparation for delivering salazosulfapyridine to the large intestine was obtained.

EXAMPLE 6

Tablet as a Preparation for Delivering Prednisolone to the Large Intestine

Prednisolone (25 parts), lactose (25 parts), crystalline cellulose (20 parts), low-substitution hydroxypropyl cellulose (25 parts) and hydroxypropyl cellulose (5 parts) were mixed and then kneaded in the presence of water. Granules were produced by treatment with a speed mill and the resulting granules were dried. The dried product (99 parts) was mixed with magnesium stearate (1 part) and tablets each weighing 200 mg were prepared in the usual manner. The tablets (300 parts) were coated with a first layer in the usual manner using a coating solution consisting of hydroxypropylmethyl cellulose phthalate (HP-55, 7 parts), purified shellac (0.7 parts), acetylated monoglyceride (0.7 parts), methylene chloride (45.8 parts) and ethanol (45.8 parts) in such a way that the solids content would be equivalent to 7.5 parts.

The tablets with the first layer (300 parts) were coated with a second layer using a dimethylaminoethyl methacrylate-methyl methacrylate copolymer (Eudragit E.30D) as a coating solution in such a way that the solids content would be equivalent to 6.0 parts.

The tablets with the first and second layers (300 parts) were then coated with a third layer using a methyl methacrylate-methacrylic acid copolymer (Eudragit L-30D 55) as a coating solution in such a way that the solids content would be equivalent to 6.0 parts.

EXAMPLE 7

Tablet as a Preparation for Delivering Prednisolone to the Large Intestine

Tablets were prepared by repeating the same procedure as in Example 6 except that 25 parts of prednisolone was replaced by 10 parts of prednisolone and 15 parts of citric acid.

EXAMPLE 8

Tablet as a System for Delivering Prednisolone to the Large Intestine

To 92.7 parts of L-ascorbic acid, an ethanol suspension containing 5 wt % of hydroxypropyl cellulose and 30 wt % of talc was added in such a way as to provide a solids content equivalent to 7.3 parts. The ingredients were kneaded, granulated with a milling granulator and dried to obtain granules for tablet.

Sixty-five parts of the resulting granules were mixed with 24.5 parts of crystalline cellulose, 10 parts of low-substitution hydroxypropyl cellulose and 0.5 parts of magnesium stearate and tablets each weighing 165 mg were produced in the usual manner.

The tablets (400 parts) were coated with a first layer in the usual manner using a coating solution consisting of hydroxypropylmethyl cellulose phthalate (HPMCP:HP-55, 3 parts), polyethylene glycol (PEG-6000, 0.6 parts) ethanol (40 parts) and methylene chloride (56.4 parts) in such a way that the solids content would be equivalent to 3.5 wt %. The tablets with the first layer (400 parts) were coated with a second layer in the usual manner using a coating solution consisting of polyvinyl acetate diethyl aminoacetate (AEA, 3 parts), talc (3 parts), PEG-6000 (0.6 parts), stearic acid (0.6 parts), ethanol (40 parts) and methylene chloride (52.8 parts) in such a way that the solids content would be equivalent to 2 wt %.

The same procedure was repeated to prepare two-layer coated tablets except that the solids content in the second layer was changed to 4 wt % or 6 wt %.

Each of the three kinds of two-layer coated tablets (400 parts) were coated with an additional layer in the usual manner using a coating solution consisting of HP-55 (3 parts), PEG-6000 (0.6 parts), stearic acid (0.6 parts), ethanol (40 parts) and methylene chloride (55.8 parts) in such a way that the solids content would be equivalent to 6 wt %, whereby a system for delivering L-ascorbic acid to the large intestine was obtained.

EXAMPLE 9

Tablet as a system for Delivering Salazosulfapyridine to the Large Intestine

Salazosulfapyridine (30 parts), tartaric acid (20 parts), crystalline cellulose (20 parts), lactose (24.5 parts), low-substitution hydroxypropyl cellulose (LH-31, 5 parts) and magnesium stearate (0.5 parts) were mixed and tablets each weighing 200 mg were prepared in the usual manner. These tablets (400 parts) were coated with a first layer in the usual manner using a coating solution consisting of HPMCP (HP-55, 2.75 parts), hydroxypropylmethyl cellulose (HPMC:TC-5, 0.25 parts), PEG-6000 (0.6 parts), ethanol (40 parts) and methylene chloride (56.4 parts) in such a way that the solids content would be equivalent to 4.5 wt %.

The tablets were then coated with a second and third layer as in Example 8, whereby a system for delivering salazosulfapyridine to the large intestine was obtained.

EXAMPLE 10

Capsule as a Preparation for Oral Administration of Erythropoietin

A solution (150 mg) of middle-chain aliphatic acid triglyceride (MCT) containing 0.01% erythropoietin was filled into hard gelatin capsules (No. 4) and a cap was sealed to the body, thereby obtaining capsules filled with erythropoietin in liquid form (which are hereinafter referred to as "capsules").

The capsules (400 g) were charged into a centrifugal granulator. While they were sprayed with an 80% ethanol solution containing 5 wt % of HPC-L under rotation, a powder mixture of crystalline cellulose (50 parts) and citric acid (50 parts) was added in an amount of 20 wt % of the capsule weight so that it was coated onto the capsule surface. Upon drying, capsules having the structure shown in FIG. 3E were obtained.

Using the resulting acid-coated capsules, the procedure of Example 9 was repeated to obtain a system for delivering erythropoietin to appropriate sites in the intestines.

EXAMPLE 11

Capsule as a Preparation for Oral Administration of rG-CSF

A solution (150 mg) of MCT containing 0.1% rG-CSF was filled into hard gelatin capsules (No. 4) and a cap was sealed to the body, thereby obtaining capsules filled with rG-CSF in liquid form.

By repeating the same procedure as in Example 10, a system for delivering rG-CSF to appropriate sites in the intestines was obtained.

Experiment 1

Granules A, B and C prepared in Example 1, 2, and 3, respectively, were subjected to a dissolution test by the second method of dissolution test (paddle method) described in the Eleventh Revised Edition of the Japanese Pharmacopoeia. The test was conducted using 900 ml of test solutions at a temperature of 37°±0.5° C. with the paddle being rotated at 100 rpm. The sample weight was 1.0 g. The test solutions were sampled at given time intervals and the amount of L-ascorbic acid in the test solutions was determined to calculate the percent dissolution. As the test solutions, JP Solutions I and II having the following formulas were used.

JP Solution I: 2.0 g of sodium chloride dissolved in 24.0 ml of dilute hydrochloric acid and water is added to make 1,000 ml.

JP Solution II: 250 ml of a 0.2M potassium dihydrogenphosphate is mixed with 118 ml of a 0.2M sodium hydroxide test solution and water is added to make 1,000 ml.

The test results are shown in Table 1, as well as in FIGS. 4 and 5. As a comparison, granules were prepared with a first

layer coated as in Example 1. In Table 1 and FIGS. 4 and 5, (A) refers to Example 1, (B) to Example 2, and (C) to Example 3.

TABLE 1

Sample	Dissolution in 2 hours	50% Dissolution time	80% Dissolution time	Lag time
A	60%	100 min.	160 min.	45 min.
B	25%	155 min.	240 min.	75 min.
C	6.5%	255 min.	300 min.	2 hours
Comparison	100%	15 min.	20 min.	5 min.

Experiment 2

Samples **1, 2, 3** which were the three kinds of tablets prepared by Example 8 were subjected to the same dissolution test as in Experiment 1. The results are shown in FIG. **6** (average for n=6).

I claim:

1. A pharmaceutical preparation for oral administration which is a granule and is adapted to release the drug at appropriate sites in the intestines, said preparation consisting of;

(a) a core that comprises erythropoietin or granulocyte colony-stimulating factor as the active ingredient and a pharmaceutically acceptable excipient;

(b) a first layer surrounding the core and which comprises an enteric ingredient consisting of hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methyl methacrylate-chloro-trimethylammonium ethyl methacrylate copolymer, cellulose acetate phthalate, cellulose propionate phthalate, cellulose acetate maleate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, styrene-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, or a water-soluble ingredient consisting of acetyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, or carboxymethyl cellulose sodium, said first layer being present in an amount of about 5–60 weight percent of the core;

(c) a second layer which is an enteric layer surrounding the first layer and which comprises a non-enteric ingredient, said layer is permeable to intestinal fluid and dissolves upon reacting with intestinal fluid combined with at least one ingredient in the core, said non-enteric ingredient of the second layer comprising polyvinyl acetate dimethyl aminoacetate, polyvinyl aminoacetal, or dimethylaminoethyl methacrylate-methyl methacrylate copolymer and, said second layer being present in an amount of about 10–30 weight percent of the core and first layer; and

(d) a third layer surrounding the second layer and which comprises an enteric ingredient, said third layer consisting cellulose acetate phthalate, cellulose propionate phthalate, cellulose acetate maleate, polyvinyl alcohol phthalate, styrene-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid/methyl methacrylate copolymer, or ethyl methacrylate-methyl methacrylate-chloro-trimethylammonium ethyl methacrylate copolymer; said third layer being present in an amount of about 10–30 weight percent of the core, first layer and second layer.

2. A pharmaceutical preparation for oral administration which is a tablet or capsule and is adapted to release the drug at appropriate sites in the intestines, said preparation consisting of;

(a) a core that comprises erythropoietin or granulocyte colony-stimulating factor as the active ingredient and a pharmaceutically acceptable excipient;

(b) a first layer surrounding the core and which comprises an enteric ingredient consisting of hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid-methyl methacrylate copolymer, ethyl methacrylate-methyl methacrylate-chloro-trimethylammonium ethyl methacrylate copolymer, cellulose acetate phthalate, cellulose propionate phthalate, cellulose acetate maleate, polyvinyl acetate phthalate, polyvinyl alcohol phthalate, styrene-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, or a water-soluble ingredient consisting of acetyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, or carboxymethyl cellulose sodium; said first layer being present in an amount of about 0.5–10 weight percent of the core;

(c) a second layer which is an enteric layer surrounding the first layer and which comprises a non-enteric ingredient, said layer is permeable to intestinal fluid and that dissolves upon reacting with intestinal fluid combined with at least one ingredient in the core, said non-enteric ingredient of the second layer comprising polyvinyl acetate diethyl aminoacetate, polyvinyl aminoacetal, or dimethylaminoethyl methacrylate-methyl methacrylate copolymer and; said second layer being present in an mount of about 0.5–10 amount weight percent of the core and first layer and

(d) a third layer surrounding the second layer and which comprises an enteric ingredient, said third layer consisting cellulose acetate phthalate, cellulose propionate phthalate, cellulose acetate maleate, polyvinyl alcohol phthalate, styrene-acrylic acid copolymer, methyl acrylate-methacrylic acid copolymer, polyvinyl acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose acetate succinate, methacrylic acid/methyl methacrylate copolymer, or ethyl methacrylate-methyl methacrylate-chloro-trimethylammonium ethyl methacrylate copolymer and, said third layer being present in an mount of about 1.0–10 weight percent of the core, first layer and second layer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,540,945

DATED : July 30, 1996

INVENTOR(S) : Heiji Ikushima

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4, line 16, "10-80 wt%" should be -- 10-30 wt% --.

Column 10, line 43, "mount" should be --amount--.

Signed and Sealed this

Thirty-first Day of December, 1996

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

[redacted]

64


US007303763B2

(12) **United States Patent**
Ho

(10) **Patent No.: US 7,303,763 B2**
(45) **Date of Patent: *Dec. 4, 2007**

(54) **COMPOSITIONS FOR CONJUGATED ESTROGENS AND ASSOCIATED METHODS**

(75) Inventor: **Thomas Ho**, Irvine, CA (US)

(73) Assignee: **Watson Laboratories, Inc.**, Salt Lake City, UT (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 784 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/668,104**

(22) Filed: **Sep. 22, 2003**

(65) **Prior Publication Data**

US 2004/0131683 A1 Jul. 8, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/076,046, filed on Feb. 12, 2002, now Pat. No. 6,630,166.

(60) Provisional application No. 60/268,177, filed on Feb. 12, 2001.

(51) **Int. Cl.**

A61K 9/36	(2006.01)
A61K 9/28	(2006.01)
A61K 9/30	(2006.01)
A61K 9/32	(2006.01)

(52) **U.S. Cl.** **424/479**; 424/474; 424/475; 424/482

(58) **Field of Classification Search** 424/474, 424/475, 479, 482

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,565,115 A		8/1951	Bates et al.
2,720,483 A		10/1955	Stiller et al.
4,309,405 A		1/1982	Guley et al.
5,395,627 A		3/1995	Dopper et al.
5,547,948 A	*	8/1996	Barcomb
5,720,977 A		2/1998	Deghenghi
5,908,638 A	*	6/1999	Huber et al.
6,346,269 B1	*	2/2002	Hsiao et al.
6,630,166 B1		10/2003	Ho

* cited by examiner

Primary Examiner—Humera N Sheikh
(74) *Attorney, Agent, or Firm*—Thorpe North & Western, LLP

(57) **ABSTRACT**

Oral conjugated estrogen formulations are disclosed and described. In one aspect, the oral formulation may be a tablet having a core and one or more coatings thereon. In addition to conjugated estrogen ingredients, the core may include one or more organic excipients and one or more inorganic excipients. In one aspect, the organic excipients may include less than about 20% w/w of a cellulose ingredient, and less than about 50% w/w of a sugar ingredient. In another aspect, the inorganic excipients may include less than about 10% w/w of a calcium phosphate tribasic ingredient. In yet another aspect, the formulation does not crack when stored at about 40° C. and about 75% relative humidity for about 2 months.

22 Claims, 2 Drawing Sheets

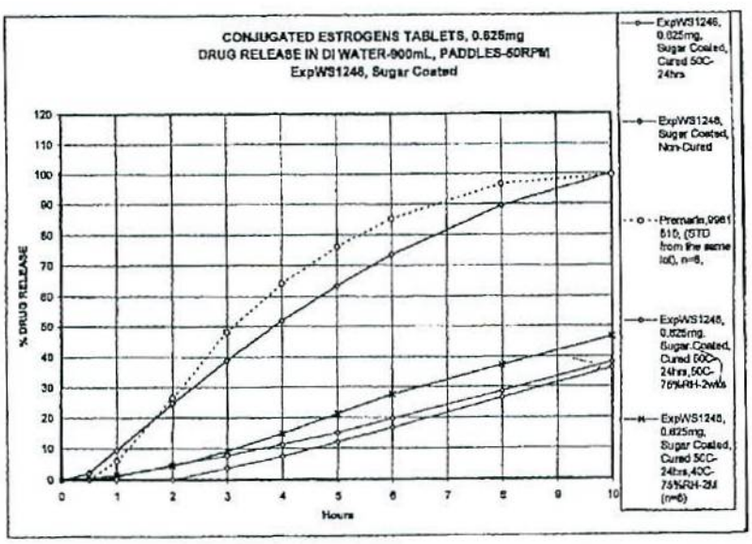


FIGURE 1

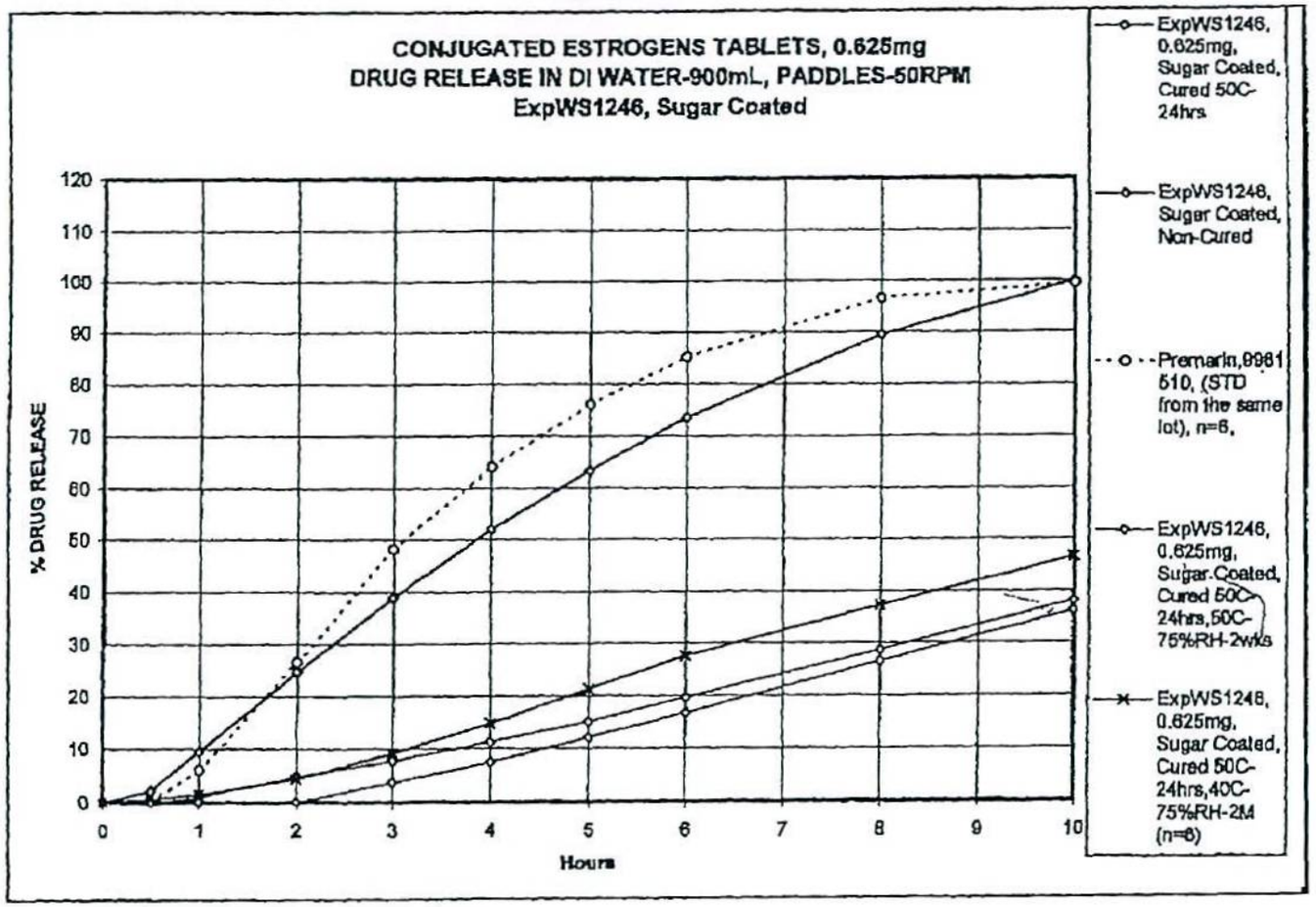
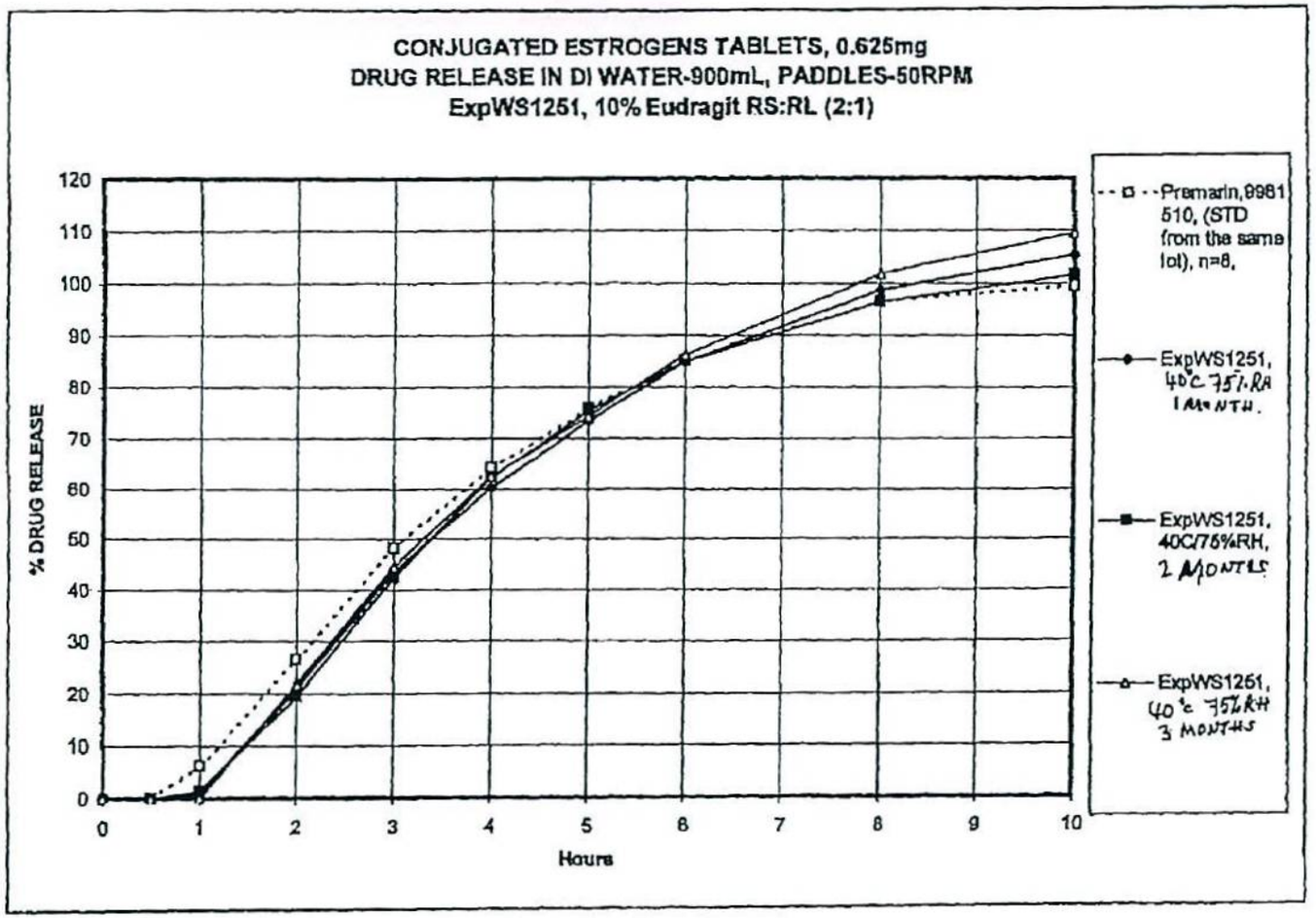

CONJUGATED ESTROGENS TABLETS, 0.625mg
DRUG RELEASE IN DI WATER-900mL, PADDLES-50RPM
ExpWS1246, Sugar Coated
% DRUG RELEASE
Hours
0
10
20
30
40
50
60
70
80
90
100
110
120
0
1
2
3
4
5
6
7
8
9
10
ExpWS1246, 0.625mg, Sugar Coated, Cured 50C-24hrs
ExpWS1246, Sugar Coated, Non-Cured
Premarin,8981510, (STD from the same lot), n=6,
ExpWS1246, 0.625mg, Sugar-Coated, Cured 50C-24hrs,50C-75%RH-2wks
ExpWS1246, 0.625mg, Sugar Coated, Cured 50C-24hrs,40C-75%RH-2M (n=6)

FIGURE 2


CONJUGATED ESTROGENS TABLETS, 0.625mg
DRUG RELEASE IN DI WATER-900mL, PADDLES-50RPM
ExpWS1251, 10% Eudragit RS:RL (2:1)
% DRUG RELEASE
Hours
0
10
20
30
40
50
60
70
80
90
100
110
120
0
1
2
3
4
5
6
7
8
9
10
Premarin,9981 510, (STD from the same lot), n=8,
ExpWS1251, 40°C 75% RH 1 MONTH.
ExpWS1251, 40C/75%RH, 2 MONTHS
ExpWS1251, 40°C 75% RH 3 MONTHS

COMPOSITIONS FOR CONJUGATED ESTROGENS AND ASSOCIATED METHODS

PRIORITY DATA

This application is a continuation-in-part of U.S. patent application Ser. No. 10/076,046, filed on Feb. 12, 2002 now U.S. Pat. No. 6,630,166, which claims priority to U.S. Provisional Patent application Ser. No. 60/268,177, filed on Feb. 12, 2001, each of which are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to conjugated estrogen formulations and methods of administering such compositions. Accordingly, this invention covers the fields of pharmaceutical sciences, medicine, cosmetics, and related sciences.

BACKGROUND OF THE INVENTION

Conjugated estrogens have been used for years as an estrogen supplement in order to treat or prevent a variety of conditions that are induced or exacerbated by estrogen hormone deficiency. Particularly, conditions experienced by peri-menopausal, menopausal, and post-menopausal women such as osteoporosis, hot flashes, vaginal atrophy, and loss of protection against heart attacks, can be ameliorated using conjugated estrogens as part of an estrogen replacement therapy routine.

Although conjugated estrogens may be administered using various routes of administration, oral tablet administration has traditionally been the most common. Such formulations have not only contained conjugated estrogens, but have also included other hormones, such as progesterone in order to balance the physiological effects of estrogen supplementation. For example, oral estrogen replacement tablets containing either a conjugated estrogen, or combination of conjugated estrogen and medroxyprogesterone acetate are currently marketed under the trade names PREMARIN®, PREMPRO™, and PREMPHASE®, by Wyeth-Ayerst Laboratories, Inc.

While oral tablet regimens of conjugated estrogen have been able to achieve acceptable therapeutic results, various drawbacks to known oral tablet formulations still exist. Example of such drawbacks include erratic drug release, degradation of the conjugated estrogen, and cracking of the tablet formulation during storage.

A variety oral tablet formulations of both instant and sustained release for administering conjugated estrogen are currently known. For example, U.S. Pat. No. 5,395,627, which is incorporated herein by reference in its entirety, discloses pharmaceutical granulates and process for making granulates to be used in oral tablet manufacture, which are very resistant to segregation, and which display an increased stability for certain steroids, such as estrogens and progestogens.

U.S. Pat. No. 5,547,948, which is incorporated herein by reference in its entirety, discloses a sugar coating composition for application to a compressed medicinal tablet used to co-deliver two or more pharmacologically-active agents. Particularly, the sugar coating composition includes sugar, a therapeutic amount of a hormonal steroid, and a hormonal steroid release-controlling amount of microcrystalline cellulose. The tablet core contains a medicinal agent which is conventionally co-delivered with the specific steroid in the sugar coating.

U.S. Pat. No. 5,720,977, which is incorporated herein by reference in its entirety, discloses an effervescent oral formulation containing a water-soluble and stable estrogen compound, such as estropipate, or estrone, a water soluble calcium salt, and a pharmaceutically acceptable excipient. The effervescent activity of the tablet is purported to aid the body's absorption of estrone and other estrogens due to their water insoluble nature. Further, the calcium component of the effervescent causing ingredients may be used as a calcium supplement to further protect against bone loss and osteoporosis.

U.S. Pat. No. 5,908,638, which is incorporated herein by reference in its entirety, discloses a solid dosage unit form containing low dose conjugated estrogens that are released at regular increments (i.e. sustained release) upon oral administration. Generally, the sustained release of estrogens and other hormones, when included, is accomplished by the inclusion of a high molecular weight hydroxypropylmethylcellulose, which may be further combined with other hydrophilic gums. In addition to controlled release, this patent discloses that strict control of moisture content within the formulation is essential to stabilizing conjugated estrogens and achieving a uniform release thereof.

In spite of the foregoing, problems such as insolubility, instability, and tablet cracking associated with oral conjugated estrogen tablets still persist. Therefore, an oral tablet formulation which overcomes, or at least ameliorates, these shortcomings continues to be sought through ongoing research and development efforts.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a pharmaceutical composition in a solid oral dosage form which does not crack after storage at about 40°C. and about 75% relative humidity for about 2 months. In other words, the compositions are stable under ambient conditions in most environments. In one aspect, the solid oral dosage form may be a tablet having a core containing a therapeutically effective amount of a conjugated estrogen, or a hormonal component thereof, at least one organic excipient, at least one inorganic excipient. A variety of specific conjugated estrogens and specific amounts thereof may be included. However, in one aspect, the conjugated estrogen may be present in an amount of from about 0.1 mg to about 3 mg. In another aspect, the amount may be about 0.625 mg.

A variety of organic excipients may be used in the core of the present oral formulation. In one aspect, the organic excipients may include less than about 25% w/w of a cellulose ingredient, and less than 50% w/w of a sugar ingredient. Further, while a variety of inorganic excipients may be used, in one aspect, the inorganic excipients may include less than about 10% w/w of a calcium phosphate tribasic ingredient.

In addition to the core recited above, the oral formulation of the present invention may include an outer coating. In one aspect, the coating may be substantially free of hormones. In another aspect, the coating may contain one or more sugar ingredients. In yet another aspect, the coating may include one or more acrylic polymers.

There has thus been outlined, rather broadly, the more important features of the invention so that the detailed description thereof that follows may be better understood, and so that the present contribution to the art may be better appreciated. Other features of the present invention will become clearer from the following detailed description of

the invention, taken with the accompanying drawings and claims, or may be learned by the practice of the invention.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1** shows a graphical representation of the comparative drug release results achieved for various sugar coated 0.625 mg dose conjugated estrogen tablets, as compared to a Premarin® tablet as a control.

FIG. **2** shows a graphical representation of the comparative drug release results achieved for various acrylic coated 0.625 mg dose conjugated estrogen tablets, as compared to a Premarin® tablet as a control.

DETAILED DESCRIPTION

Before the present invention is disclosed and described, it is to be understood that this invention is not limited to the particular structures, process steps, or materials disclosed herein, but is extended to equivalents thereof as would be recognized by those ordinarily skilled in the relevant arts. It should also be understood that terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting.

Definitions

In describing and claiming the present invention, the following terminology will be used.

The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a polymer" includes reference to one or more types of polymers, and reference to "an estrogen" includes reference to one or more types of estrogen.

The term "formulation" and "composition" may be used interchangeably herein.

The phrases "therapeutically effective amount" refers to an amount of conjugated estrogen sufficient to achieve therapeutic or adequate hormone supplementation results. The determination of an effective amount is well within the ordinary skill in the art of pharmaceutical, cosmetic, and medical sciences. See, for example, Meiner and Tonascia, "Clinical Trials: Design, Conduct, and Analysis," *Monographs in Epidemiology and Biostatistics*, Vol. 8 (1986), incorporated by reference in its entirety.

As used herein, "free of" and "substantially free of" refer to the absence of a specific agent or compound, or if present, such agent or compound is present in an amount that does not provide its functional purpose to a measurable degree. For example, a tablet coating that is "free of," or "substantially free of" a hormone may be either totally hormone free, or contain such a minute amount of hormone, so as to provide no measurable physiological effect. In some cases, the phrase "completely free of" may be used to indicate the complete and total absence of a specific agent or compound.

The term "administration" refers to oral delivery of conjugated estrogen. This method and other methods of administration are well known to those in the pharmaceutical arts.

The term "cellulose" refers to a polysaccharide consisting of anhydroglucose units joined by an oxygen linkage to form long molecular chains that are essentially linear. A number of specific cellulose inclusive compounds are known and used as excipients in the pharmaceutical arts, including without limitation, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxybutylethylcellulose, hydroxybutylmethylcellulose, ethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, as well as other cellulose derivatives. As such, the recitation of the term "cellulose" generically, should be interpreted to include such specific cellulosic compounds, as well as others not expressly recited.

The term "sugar" refers to any type of simple carbohydrate, such as a mono or disaccharide, or a combination thereof, either naturally obtained, refined from a natural source, or artificially produced. A variety of sugars are known and used in various pharmaceutical formulations, including without limitation, sucrose, glucose, mannose, fructose, lactose, etc. As such, the recitation of the term "sugar" generically, should be interpreted to include such specific compounds, as well as others not expressly recited.

Concentrations, amounts, solubilities, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited.

As an illustration, a concentration range of "about 1% w/w to about 10% w/w" should be interpreted to include not only the explicitly recited concentration of about 1% to about 10% w/w, but also include individual concentrations and the sub-ranges within the indicated range. Thus, included in this numerical range are individual concentrations such as 2% w/w, 5% w/w, and 8% w/w, and sub-ranges such as from 1% w/w to 3% w/w, from 2% w/w to 4% w/w, from 3% w/w to 8% w/w, from 5% w/w to 9% w/w, from 1% w/w to 7% w/w etc. The same principle applies to ranges reciting only one numerical value.

Similarly, an open ended range recited as "less than about 10% w/w" should be interpreted to include all of the values and ranges as elaborated above for the range of "from about 1% w/w to about 10% w/w." Furthermore, it is understood that functional limitations may exist for limits not expressly recited by an open ended range, and that such limitations are inherently included as part of the disclosure of the present application, though not expressly recited. Such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

Invention

The present invention relates to a formulation comprising a core containing conjugated estrogens, one or more inorganic excipients, one or more organic excipients, and one or more fillers, and a coating comprising either a sugar or one or more acrylic polymers and/or copolymers. The oral dosage formulation of the present invention includes in one aspect, a tablet having a core and a coating. The tablet may be made in accordance with a variety of techniques known to those skilled in the pharmaceutical arts. For example, the core may contain a simple admixture of particulate, or beaded ingredients, as is known, or beads may be provided that have specific configurations, such as an inner center of excipient, surrounded by a conjugated estrogen. Other possible core configurations will be readily recognized by those skilled in the art.

The conjugated estrogens of the present invention are those generally known and described in the art as conjugated estrogens. See United States Pharmacopia (USP 23). While conjugated estrogens are typically a mixture of estrogenic components, such as estrone and equilin, the present invention may be formulated to either utilize such a mixture, or to include only selected or individual estrogenic components. These conjugated estrogens may be of synthetic or natural origin. Naturally occurring conjugated estrogens are

obtained from pregnant mare urine and then are processed and may be stabilized. Examples of such processes are set forth in U.S. Pat. Nos. 2,565,115 and 2,720,483, each of which are incorporated herein by reference. Many conjugated estrogen products are now commercially available.

Conjugated estrogens are also made synthetically. Examples of synthetically produced estrogens include estropipate and ethinyl estradiol. "Conjugated estrogens" as used herein includes both natural and synthetic conjugated estrogens, such as the Pharmacopia inclusive compounds alluded to above, as well as other estrogens so considered by those skilled in the art. Further, "conjugated estrogens" refers to esters of such compounds, such as the sulfate esters, salts of such compounds, such as sodium salts, and esters of the salts of such compounds, such as sodium salts of a sulfate ester, as well as other derivatives known in the art. Some specific examples include: 17-alpha and beta-dihydroequilin, equilenin, 17-alpha and beta-dihydroequilenin, estrone, 17-beta-estradiol, and their sodium sulfate esters.

The specific conjugated estrogen dose included in the tablet of the present invention may be any dosage required to achieve a specific therapeutic effect, and may vary depending on the specific treatment indicated, and on the specific conjugated estrogen included in the tablet. However, in general, dosages of conjugated estrogens included in the tablet, can range from about 0.2 mg/tablet to about 3.0 mg/tablet.

In addition, the present dosage forms can include other hormones such as progestins and androgens. Such hormones may be incorporated either into the core or coating of the present tablet, as discussed further below. Specific progestins that may be used include without limitation: progesterone, medroxyprogesterone, and a variety of synthetic progestins and their salts, esters, and derivatives that are generally known and used in the oral contraceptive area. Specific androgens that may be used, include without limitation, testosterone, methyltestosterone, and other known derivatives and their esters and salts, including deconoate, cypionate, propionate, etc. Any of these hormones can also be micronized.

The inorganic excipients include calcium phosphate tribasic, and calcium carbonate. The calcium phosphate tribasic is present at less than about 20% of the weight of the composition. In some aspects, the calcium phosphate tribasic is present at less than about 15% by weight; in some aspects, less than about 10% by weight; in some aspects, it is less than 8% by weight; and in some aspects, it is less than 5% by weight of the composition. In another aspect, the calcium phosphate tribasic ingredient may be present in an amount of from about 0.5% by weight to about 20% by weight. In one aspect, it has been discovered that when the calcium phosphate tribasic is present at these proportions, the physical stability of the composition is greatly increased during storage, for example by reduced cracking, as compared to those compositions of U.S. Pat. No. 5,908,638.

The invention also comprises one or more organic excipients in the tablet core, such as a cellulose ingredient. In one aspect, the cellulose may be hydroxypropylmethylcellulose. Other excipients that can be used in the core of the composition include without limitation: hydroxypropyl cellulose, carboxymethylcellulose, ethyl cellulose, methyl cellulose, their derivatives and salts, as well as mixtures thereof. Additionally, other organic excipients, such as polyethylene glycol, talc, lactose, starch, sorbitol, mannitol, polyvinylpyrrolidone can also be used.

In one particular aspect, lactose, or another sugar may be included in the core, wherein the lactose, or other sugar is present at less than about 50% by weight of the formulation. In one aspect, the lactose, or other sugar may be present in an amount of from about 1% to about 50% by weight. In some aspects, the amount may be from about 10% to about 50% by weight; in some aspects, from about 10% to about 40%; in some other aspects, from about 10% to about 30% by weight; in yet other aspects, from about 5% to about 30% by weight; in yet some other aspects, from about 5% to about 50% by weight. In one aspect, the amount may be from about 20% to about 30% by weight.

Notwithstanding the above-recited core ingredients and amounts therefore, in one aspect, the tablet of the present invention may include gel forming excipients, such as various celluloses and gelatins, in an amount of less than about 25% w/w of the composition. In use, such excipients form a gel in an aqueous solution, and therefore, when the tablet coating is penetrated by digestive fluids, the core swells and ruptures the coating to facilitate release of the conjugated estrogen. In another aspect of the invention, the amount of gel forming excipients may be less than about 20% w/w of the composition. In yet another aspect, the amount may be less than about 15% w/w of the composition. In a further aspect, the amount may be from about 1%-25% w/w.

The coating for the tablet of the present invention may be made from a wide variety of materials including sugars and acrylic polymers and copolymers. Of particular note is that in one aspect, no hormones are contained in the coating. In other aspects, the coating may contain hormones in addition to a variety of other ingredients known to those skilled in the art, such as plasticizers, colorants, and solvents or other vehicles. Notably, such ingredients create a barrier that is initially soluble in gastrointestinal fluid, in order to achieve an initial drug release. By contrast, many sustained release formulations, such as the formulation disclosed in U.S. Pat. No. 5,908,638 require that the tablet coating provide a coating that is impervious to stomach fluid for at least the first few hours. As such, in one aspect, the tablet of the present invention may include a coating that provides initial drug release while in the stomach of a subject. In another aspect, initial drug release may occur in less than about 2 hours after administration. In yet another aspect, initial drug release may occur in less than about 1 hour after administration.

A wide variety of sugars may be used for the coating of the present invention as known to those skilled in the art. Examples of suitable sugars include without limitation, sucrose derived from a variety of sources, such as beet or cane sources, starch, saccharide or polysaccharide converted sources, and which is considered suitable for use in pharmaceutical applications.

A number of acrylic polymers or copolymers known to those skilled in the art may also be used to form the coating of the tablet of the present invention. Examples of specific polymers include without limitation, polymers of acrylic esters, such as methacrylate, and methyl methacrylate copolymers. Various acceptable polymers may be obtained from a variety of commercial sources, such as EUDRAGIT® polymers available from Rohm and Haas Corporation. In one aspect, the coating may include a mixture or blend of acrylic polymers or copolymers. In another aspect, the mixture may be present at a ratio of from about 1:10 to about 10:1. In a further aspect, the ratio may be from about 1:5 to 5:1. In yet another aspect, the ratio may be from about 1:2 to about 2:1.

The present invention is distinct from the previously known and/or disclosed formulations in at least the following ways:

a) in the presence of lactose or similar sugar excipient in an amount of about or less than 50% by weight; or from about 1%-50% by weight; or from about 5%-50% by weight, or from about 10%-40% by weight, or from about 10%-30% by weight; or from about 20%-30% by weight;

b) in the presence of calcium phosphate tribasic in an amount of less than 20% by weight; or from about 0.5%-20% by weight; or from about 5%-20% by weight; or from about 5%-15% by weight; or from about 1%-15% by weight; or from about 1%-10% by weight; or from about 5%-10% by weight;

c) in the absence of a substantial amount of a hormone in the outer coating layer in some embodiments;

d) in the absence of a substantial amount of a microcrystalline cellulose in the outer coating layer to aid in controlling the release of the drug from the core;

e) in the absence of a substantial amount of a moisture barrier imparting polymer (i.e. ethyl cellulose) as an outer coat that prevents dissolution in the gastrointestinal fluid of the stomach, and therefore prevents of minimizes drug release in the stomach; and

f) in the presence of gel forming excipients in an amount of less than about 25% w/w of the composition; 20% w/w of the composition, 15% w/w, or from about 1% w/w to about 25% w/w of the composition.

It has been discovered that when the composition for conjugated estrogens comprises the above distinct characteristics, the composition does not crack over long storage times, provides a drug release that is very comparable to the commercially successful product known an Premarin®, and yet is simple to prepare. The prior known or disclosed compositions, although used commercially, have lacked one or more of the above characteristics and therefore have the need to be improved for optimal stability and patient acceptance.

More specifically, U.S. Pat. No. 5,547,948 discloses a core comprising conjugated estrogens and excipients and a sugar coat that also comprises a hormone and microcrystalline cellulose to control the release of the hormone from the coating. The invention in the '948 patent is directed at delivering the hormone in the sugar coating, and does not teach or suggest compositions that deliver conjugated estrogens from the core wherein such compositions comprise inorganic excipients such as calcium phosphate tribasic and yet that do not crack. In contrast, the present invention does not comprise a sugar coating that controls the release of the hormone.

U.S. Pat. No. 5,395,627 teaches hormonal dosage forms wherein the core is made up of desogestrel, ethinylestradiol, and lactose and polyvinylpyrrolidone, among others, and a film coat comprising HPMC and PEG. The specification teaches diluents such as lactose from about 70% to about 95% by weight of the composition and does not teach the inclusion of conjugated estrogens. In contrast, the excipients of the present invention comprise lactose at about or less than about 50% by weight and contain an inorganic excipient such as calcium phosphate tribasic and comprise conjugated estrogens.

U.S. Pat. No. 5,720,977 teaches formulations comprising estropipate, calcium glycerophosphate, citric acid, and sodium bicarbonate to provide effervescence. Estropipate, which can also be used in the present invention, is admittedly distinct from naturally occurring conjugated estrogens in that the latter are highly moisture sensitive, whereas estropipate is known to be "stable." See, column 3, lines 17-25.

U.S. Pat. No. 5,908,638 teaches that in order to accomplish stable conjugated estrogen formulations: a) the moisture content must be less than 2.5% free water; b) inorganic excipients should not be present; c) shellac coating should be avoided; c) the core tablets must be coated using a moisture barrier material. See, columns 7, 8, 10, and 14. This patent teaches that water bound to organic excipients do not cause any deleterious effects to the conjugated estrogens. See column 8, lines 39-41.

In contrast to these teachings, the present invention comprises an inorganic excipient, in some embodiments a shellac coating, and does not contain a moisture barrier coating. Rather, only a sugar coating or an acrylic coating is used. Further, it is believed, without wishing to be bound by any theory, that the particular combination of one or more of the above unique characteristics result in conjugated estrogen formulations that deliver the drug at rates comparable to the commercially successful Premarin® formulation. Further, such a formulation is stable and does not crack on extended storage, such as for one month, or two months or longer, under accelerated stability temperature and humidity conditions. Or, of a more practical nature, as indicated by passing accelerated stability tests, the compositions of the present invention are stable and do not crack over an extended period of time under ambient conditions of temperature and humidity as found in various environments.

One contributing factor to the success of the present inventions may be, again without wishing to be bound by any theory, the presence of lactose in lower amounts (i.e., at about or less than 50% by weight and other amounts disclosed herein) than in the previously disclosed formulations of conjugated estrogens. Another contributing factor may be, again without wishing to be bound by any theory, the presence of low amounts (less than or about 20% by weight or other amounts as disclosed herein) of calcium compound such as calcium phosphate tribasic. It is also possible that one or more of these factors taken either alone, or in combination contribute to the desired physical characteristics described above.

A variety of conventional methods known to those skilled in the art may be used to produce the tablets of the present invention. Examples of such methods, such as wet granulation, fluid-bed granulation, dry granulation, and direct compression may be found in *Remmington's Pharmaceutical Sciences* pp. 1615-1649 (19th ed. 1995).

EXAMPLE 1

The active bulk ingredients were weighed and comminuted with hydroxypropylmethyl cellulose (Methocel K-3) under nitrogen atmosphere. The mixture was passed through a #20 mesh screen. The resulting mixture was blended with dehydrated alcohol under nitrogen atmosphere and dried with a loss on drying no greater than 2.5%. The dried mixture was then again passed through a Mesh #20 screen. The mixture was then blended with calcium phosphate tribasic, lactose (Fast-flo316) and microcrystalline cellulose (Avicel PH 113), again under nitrogen atmosphere. This mixture was further treated with stearic acid and magnesium stearate as lubricants. The resulting blend was dried again with a loss on drying no more than 2.5%. The dried mixture was then compressed into tablets on a rotary tablet press.

EXAMPLE 2

Tablets prepared as in Example 1, and having a core composition as shown in Table 1, were placed in a 24" Accelacota Side Vented coating pan and coated with shellac. This was followed by a coating of sugar. The resulting sugar-coated tablets were cured for 24 hours in a Nary oven at 50° C. The composition of the sugar-coated tablets is given in the following Table 1.

TABLE 1

Composition of sugar-coated 0.625 mg conjugated estrogens tablets

Ingredient	Mg/tablet
CORE	
Conjugated estrogens	0.625
Methocel K-3 Prem. LV	40.0
Lactose (Fast-flo316)	55.5
Calcium Phosphate Tribasic, USP	7.0
Avicel PH 113	26.0
Stearic Acid	0.65
Magnesium Stearate NF	0.65
#4 Refined Pharmaceutical Glaze, NF in 45/200 Alcohol	7.2 (solid)
Talc, USP (Alphafil 500)	7.2
COATING	
Sucrose, NF	111.3
Calcium Sulfate, NF	6.23
Talc, USP	2.25
PEG 8000, USP	0.09
Carnuba Wax, NF	0.15
Total	264.8 mg/tablet

EXAMPLE 3

Tablets as prepared in Example 1, and having the core composition as in Table 2, were placed in a 24" Accelacota Side Vented coating pan and coated with methacrylic acid copolymers. Such copolymers are commercially known as Eudragit RL30D and Eudragit RS30D. The resulting acrylic-coated tablets were cured for 24 hours in a Nary oven at 50° C. The composition for the acrylic coated tablets is given in the following Table 2.

TABLE 2

Composition of acrylic-coated 0.625 mg conjugated estrogens tablets

Ingredient	Mg/tablet
CORE	
Conjugated estrogens	0.625
Methocel K-3 Prem. LV	40.0
Lactose (Fast-flo316)	55.5
Calcium Phosphate Tribasic, USP	6.5
Avicel PH 113	26.0
Stearic Acid	0.65
Magnesium Stearate NF	0.65
Talc, USP (Alphafil 500)	5.35
COATING	
Eudragit RS-30D	4.88 (solid)
Eudragit RL-30D	2.44 (solid)
Triethyl citrate	0.33
Antifoam	0.70
Opadryl, Clear (YS-1-10925-A)	1.3
Total	144.9 mg/tablet

EXAMPLE 4

Stability and drug release rates were studied for sugar-coated tablets as prepared in Example 1 and Table 1. Stability was monitored under different storage conditions. These conditions included: 50° C., 75% relative humidity, after two weeks; 40° C., 75% relative humidity, after one month; 40° C., 75% relative humidity, after two months. The samples were monitored for various active compounds and degradation products as specified in the USP. The data are shown in Table 3. These data indicate that the sugar-coated tablets of the present invention were stable under all these accelerated conditions. This is established by the fact that the various active compounds and the degradation products were within the specified limits for USP.

TABLE 3

0.625 mg Coated (Sugar) Tablets

Conjugated Estrogens-Stability Studies
Product: 0.625 mg Coated Tablets
Lot # EXPWS 1246
Coating

		R&D s/n						
		001659	001752		002163		002300	
		Storage Condition						
		Initial	50c, 75% RH/2 wks		40c, 75% RH/1 mnth		40c, 75% RH/2 mnth	
	USP limits	% Found	% Found	% Initial	% Found	% Initial	% Found	% Initial
Estrone	52.5-61.5%	49.1	50.8	103.5	50.2	102.2	50.2	102.2
Equilin	22.5-30.5%	22.7	23.3	102.6	23.0	101.3	23	101.3
Estrone + Equilin	79.5-88.0%	71.8	74.0	103.1	73.2	101.9	73.2	101.9
17a-dihydroequilin	13.5-19.5%	14.0	14.5	103.6	14.3	102.1	14.5	103.6
17a-estradiol	2.5-9.5%	3.8	3.8	100.0	3.9	102.6	3.9	102.6
17b-estradiol	<2.25%	0.60	0.59	98.3	0.56	93.3	0.62	103.3

TABLE 3-continued

0.625 mg Coated (Sugar) Tablets

Conjugated Estrogens-Stability Studies
Product: 0.625 mg Coated Tablets
Lot # EXPWS 1246
Coating

		R&D s/n						
		001659	001752		002163		002300	
		Storage Condition						
		Initial	50c, 75% RH/2 wks		40c, 75% RH/1 mnth		40c, 75% RH/2 mnth	
	USP limits	% Found	% Found	% Initial	% Found	% Initial	% Found	% Initial
17b-dihydroequilin	0.5-4.0%	1.3	1.3	100.0	1.3	100.0	1.4	107.7
17a-dihydroequilenin	<3.25%	2.05	2.19	106.8	2.16	105.4	2.2	107.3
17b-dihydroequilenin	<2.75%	0.56	0.63	112.5	0.58	103.6	0.44	78.6
d8,9 dehydroesterone	<6.25%	4.72	4.91	104.0	4.68	99.2	4.53	96.0
Equilenin	<5.5%	2.6	2.8	107.7	2.8	107.7	2.8	107.7
Equilin/Estrone	0.35-0.65%	0.46	0.48	100.0	0.46	100.0	0.46	99.7
LOD %		1.15	1.79		1.55		1.33	

EXAMPLE 5

Stability and drug release rates were studied for acrylic-coated tablets made in accordance with Example 1 and Table 2. Stability was monitored under different storage conditions. These conditions included: 50° C., 75% relative humidity, after two weeks; 40° C., 75% relative humidity, after one month; 40° C., 75% relative humidity, after two months. The samples were monitored for various active compounds and degradation products as specified in the USP. The data are shown in Table 4. These data indicate that the acrylic-coated tablets of the present invention were stable under all these accelerated conditions. This is established by the fact that the various active compounds and the degradation products were within the specified limits for USP.

TABLE 4

0.625 mg Coated (acrylic) Tablets

Conjugated Estrogens-Stability Studies
Product: 0.625 mg Coated Tablets
Lot # EXPWS 1251
Coating 10% Eudragit/RS:RL (2:1)

		R&D s/n									
		001560	01656		001767		020874		002298		
		Storage Condition									
		Initial	50c, 75% RH/2 wks		40c, 75% RH/1m		40c, 75% RH/2m		40c, 75% RH/3m		
	USP limits	% Found	% Found	% Initial	% Found	% Initial	% Found	% Initial	% Found	% Initial	Change
Estrone	52.5-61.5%	55.9	55.2	98.7	56.6	101.3	55.9	100.00	56.4	100.9	0.5
Equilin	22.5-30.5%	27.3	26.5	97.1	27.1	99.3	26.5	97.1	26.4	96.7	0.9
Estrone + Equilin	79.5-88.0%	83.2	81.7	96.2	83.6	100.5	82.4	99.0	82.9	99.6	0.3
17a-dihydroequilin	13.5-19.5%	17.9	17.4	97.2	17.9	100.0	17.6	98.3	18.1	101.1	−0.2
17a-estradiol	2.5-9.5%	4.6	4.5	97.8	4.7	102.2	4.7	102.2	4.8	104.3	−0.2
17b-estradiol	<2.25%	1.26	1.11	88.1	0.90	71.4	0.96	76.2	0.88	69.8	0.38
17b-dihydroequilin	0.5-4.0%	2.3	2.2	95.7	2.6	108.7	2.4	104.3	2.4	104.3	−0.1
17a-dihydroequilenin	<3.25%	1.65	1.79	108.5	2.03	123.0	2.34	141.8	2.82	170.9	−1.17
17b-dihydroequilenin	<2.75%	0.77	0.67	87.0	0.97	126.0	0.86	111.7	0.68	88.3	0.09
d8,9 dehydroesterone	<6.25%	4.15	4.07	98.1	4.13	99.5	4.02	96.9	3.91	94.2	0.24
Equilenin	<5.5%	2.2	2.5	113.6	2.3	104.5	2.6	118.2	3.0	136.4	−0.8
Equilin/Estrone	0.35-0.65%	0.49	0.48	98.0	0.48	97.6	0.47	96.7	0.47	95.6	0.02
LOD %		2.52	2.35		2.94		3.04		3.18		

EXAMPLE 6

The drug release profile was obtained for the sugar-coated conjugated estrogen tablets of the present invention. Standard USP methodology was followed, which included using distilled water (900 ml), paddles at 50 rpm. The data were displayed graphically as shown in FIG. **1**. A positive control of Premarin® was used to validate further the data.

These data indicate that at least some sugar-coated tablets of the present invention release under some conditions the conjugated estrogens at approximately the same rate as the Premarin® product.

EXAMPLE 7

The drug release profile was obtained for the acrylic-coated conjugated estrogen tablets of the present invention. Standard USP methodology was followed, which included using distilled water (900 ml), paddles at 50 rpm. The data were displayed graphically as shown in FIG. **2**. A positive control of Premarin® was used to validate further the data.

These data indicate that acrylic-coated tablets of the present invention release the conjugated estrogens at approximately the same rate as the Premarin product®. This release rate is noted to be closer for all conditions tested.

Of course, it is to be understood that the above-described arrangements are only illustrative of the application of the principles of the present invention. Numerous modifications and alternative arrangements may be devised by those skilled in the art without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity and detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention, it will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function and manner of operation, assembly and use may be made without departing from the principles and concepts set forth herein.

What is claimed is:

1. A pharmaceutical composition in a solid oral dosage form comprising:

a core containing a therapeutically effective amount of at least one conjugated estrogen, or a component thereof, and at least one organic excipient, wherein the at least one organic excipient comprises less than about 25% w/w of a cellulose ingredient, and less than about 50% w/w of a sugar ingredient, and at least one inorganic excipient, wherein the at least one inorganic excipient comprises a calcium phosphate tribasic ingredient in an amount of less than about 20% w/w; and

a pharmaceutically acceptable coating that is free of hormones, wherein the composition does not crack when stored at 40° C. and 75% relative humidity for about two months.

2. The pharmaceutical composition of claim **1**, wherein the therapeutically effective amount of conjugated estrogen is from about 0.1 mg to about 3 mg.

3. The pharmaceutical composition of claim **2**, wherein the amount is about 0.625 mg.

4. The pharmaceutical composition of claim **1**, wherein the coating is a sugar coating.

5. The pharmaceutical composition of claim **1**, wherein the coating is an acrylic coating.

6. The pharmaceutical composition of claim **1**, wherein the sugar ingredient is present in an amount of from about 5% w/w to about 50% w/w.

7. The pharmaceutical composition of claim **1**, wherein the sugar ingredient is present in an amount of from about 10% w/w to about 40% w/w.

8. The pharmaceutical composition of claim **1**, wherein the sugar ingredient is present in an amount of from about 20% w/w to about 30% w/w.

9. The pharmaceutical composition of claim **1**, wherein the calcium phosphate tribasic ingredient is present in amount of from about 1% w/w to about 15% w/w.

10. The pharmaceutical composition of claim **1**, wherein the calcium phosphate tribasic ingredient is present in amount of from about 5% w/w to about 15% w/w.

11. The pharmaceutical composition of claim **1**, wherein the calcium phosphate tribasic ingredient is present in amount of from about 1% w/w to about 10% w/w.

12. The pharmaceutical composition of claim **1**, wherein the calcium phosphate tribasic ingredient is present in an amount of from about 5% w/w to about 10% w/w.

13. The pharmaceutical composition of claim **1**, wherein the conjugated estrogen is of a natural origin.

14. The pharmaceutical composition of claim **1**, wherein the conjugated estrogen is of a synthetic origin.

15. The pharmaceutical composition of claim **1**, wherein the conjugated estrogen is a mixture of estrogenic components.

16. The pharmaceutical composition of claim **1**, wherein the conjugated estrogen is an ester of an estrogen.

17. The pharmaceutical composition of claim **1**, wherein the cellulose ingredient is a member selected from the group consisting of: hydroxypropyl cellulose, carboxymethylcellulose, ethyl cellulose, methyl cellulose, salts thereof, derivatives thereof, and mixtures thereof.

18. The pharmaceutical composition of claim **17**, wherein the cellulose ingredient is hydroxypropyl cellulose.

19. The pharmaceutical composition of claim **1**, wherein the sugar ingredient is a member selected from the group consisting of: sucrose, glucose, mannose, fructose, lactose, and mixtures thereof.

20. The pharmaceutical composition of claim **19**, wherein the sugar ingredient is sucrose.

21. The pharmaceutical composition of claim **20**, wherein the sucrose is derived from a source selected from the group consisting of: beet sources, cane sources, starch, saccharide converted sources, polysaccharide converted sources, and mixtures thereof.

22. The pharmaceutical composition of claim **21**, wherein the sucrose is derived from cane sources.

* * * * *


US007544370B2

(12) **United States Patent**
Venkata Ramana Rao et al.

(10) **Patent No.: US 7,544,370 B2**
(45) **Date of Patent: Jun. 9, 2009**

(54) **PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Pantoprazole sodium multiparticulates are described which avoid sticking to nasogastric and gastronomy tubes. The pantoprazole multiparticulates have a spheroid core of pantoprazole or an enantiomer thereof, or a salt thereof, a surfactant, and a distintegrant; a sub coat which is comprised of hydroxypropyl methylcellulose (hypromellose) and water, an enteric coat on the sub-coat, and a final seal coat over the enteric coat, which is composed of hydroxypropyl methylcellulose (hypromellose) and water.

22 Claims, No Drawings

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PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit under 35 USC 119(e) of prior U.S. Provisional Patent Application No. 60/507,810, filed Oct. 1, 2003.

BACKGROUND OF THE INVENTION

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole, is a H+/K+-adenosine triphosphate (ATP) inhibitor (also known as acid pump or proton pump inhibitor (PPI), is an enzyme present in the gastric parietal cells. It is believed that these drugs are metabolized in the parietal cells to active sulfenamide metabolites that inactivate the sulfhydryl group of the proton pump, thus reducing the hydrogen ion secretion. PPIs are generally lipophilic weak bases with poor aqueous solubility at low pH. Many PPIs are unstable in low pH solutions and undergo rapid acid-catalyzed degradation, and they are relatively stable at neutral or high pH.

The current commercial oral formulations of sodium pantoprazole are single unit coated tablets. See, e.g., U.S. Pat. No. 5,997,903, which describes oral forms of pantoprazole that consist of a core, an intermediate layer and an outer layer. The current coating has a tendency to cause undesirable sticking of the tablet to the gastrointestinal tract.

Multiparticulate formulations, because of their nature of dispersing in the gastrointestinal tract, show a reduced food effect and variability in gastric emptying times, thereby providing for reduced inter and intra subject variability, as compared to single unit tablets (Intl. Journal of Pharmaceutics 140 [1996] 229-235).

Several unsuccessful attempts have been made in the past to develop a multiparticulate formulation of pantoprazole. However, these attempts yielded multiparticulates that were not bioequivalent to tablets, only 70% relative bioavailability was found. Another attempt using different technologies-non-pareil seed coating and extrusion/spheronization, resulted in a product that did not provide the appropriate release in acid conditions. In addition, these attempts yielded product that was unstable, as observed by discoloration, when stored at room temperature.

SUMMARY OF THE INVENTION

The invention provides a stable multiparticulate pantoprazole formulation that provides reduced inter and intra subject variability.

In one embodiment, the pantoprazole multiparticulates of the invention is composed of a spheroid core comprising pantoprazole or an enantiomer thereof, or a salt or hydrate thereof, at least one surfactant, at least one distintegrant, and about 1% to about 2% w/w water; an enteric coat on the core, said enteric coat comprising a copolymer of methacrylic acid and methacrylates in the range of about 15 to about 45% w/w of the spheroid core; wherein said multiparticulates have an average size of about 1 mm in diameter.

Advantageously, the multiparticulate formulations of the invention are stable under room temperature storage conditions for at least twelve months. Based on the trend analysis using the twelve month room temperature data and 6 month 40° C./75% relative humidity (RH) data available to date, the multiparticulates of the invention should have a shelf life of over 2 years. Typically, a multiparticulate formulation of the invention is considered stable if it retains 90% to 110% of its potency during shelf life storage.

This pantoprazole multiparticulate formulation of the invention is less prone to adherence to the intestinal walls, nasogastric and gastromy tubes, and pouch material thereby giving predictable delivery of the drug product to the site of drug release. It also provides for an early onset of action for relief of gastro-intestinal pain and has a prolonged duration of action. This formulation allows dosing to pediatric patients and patients who have difficulty swallowing solid foods. This formulation also allows for drug delivery via nasogastric and gastrostomy tubes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a multiparticulate formulation of pantoprazole having a unique combination of excipients and a surfactant (e.g., polysorbate 80) that are compatible with pantoprazole sodium in the presence of an alkaline pH environment. Further, the invention provides a process that utilizes low shear during granulation and low temperature during drying for preparation of the multiparticulate. This process contributes to the stability of the core of the multiparticulates of the invention.

In one aspect, the invention provides multiparticulate formulations of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, i.e., in the lower gastrointestinal tract.

The multi particulate formulation of sodium pantoprazole of the invention provides an enhanced system for the delivery of pantoprazole to patients. The current marketed formulation is a single monolithic tablet. The present formulation of multiparticulate spheroids, which is adaptable for use in a capsule or a foil packet, can be prepared by extrusion/spheronization plus coating technology.

The composition of the multiparticle of the invention, and the enteric coat, e.g., Eudragit, allows for reduced release at low pH (~1) and fast release at a neutral pH (~7). This provides faster blood levels of the drug, in patients, and thereby a faster onset of action. The smaller T_{lag} value of multiparticulate formulation as compared to that of a single monolithic tablet based on the results from dog data indicates faster onset of action of multiparticulate formulation.

The use of a multi particulate formulation facilitates dosing to pediatric patients and patients who have trouble swallowing, by dispersing the spheroids in a suspending liquid or sprinkling/dispersing in a low pH liquid like applesauce, prior to administration. The suspending liquid could be made prior to administration by mixing a blend of powder material with water. The smaller size of the multi particulates, in a capsule or pouch or any other container, also allows dosing through nasogastric or gastrostomy tube.

This formulation allows for a faster relief of GI pain, and prolonged duration of action (extended release), as compared to the current marketed tablet.

I. Multiparticulates of the Invention

Suitably, the multiparticles are in the range of about 0.1 to 2 mm, or 0.5 mm to 1.5 mm, or 0.7 mm to 1.25 mm, or 0.8 mm to 1 mm. In one embodiment, the multiparticulates in a composition of the invention average about 1 mm in diameter. Typically, the multiparticles of the invention are no greater than about 1 mm in size in order to facilitate passage through nasogastric tubes.

The multiparticulates of the invention are composed, at a minimum, of a spheroid core with an enteric coat over the core. In between the core and enteric coat an initial seal coat may be applied, e.g., comprising a coating of hydroxylpropyl methylcellulose (hypromellose). Also, over the enteric coat a final seal coat may be applied, e.g., a coating of hydroxylpropyl methyl cellulose (hypromellose). The spheroid core is composed of, at a minimum, a pantoprazole or a salt thereof, and a surfactant.

As used herein unless the context requires otherwise, the term 'pantoprazole' refers to 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole and enantiomers thereof and the term 'pantoprazole compound' includes pantoprazole and enantiomers and salts and hydrates thereof. The active compound, pantoprazole is described in European Patent 166 287, which describes the preparation thereof, and is available commercially under the brand name PROTONIX®. Examples of pharmaceutically acceptable salts of pantoprazole include, e.g., sodium, magnesium, and calcium, among others; still others are described in the European Patent 166 286, which is incorporated by reference herein. The selection of a suitable salt is not a limitation of the invention. In one embodiment, the salt is sodium. Typically, the pantoprazole compound is present in the range of from about 5 to 50% w/w, more preferably about 20 to 45% w/w, of the total multiparticulate.

Suitable surfactants are known to those of skill in the art. However, particularly desirable are sodium lauryl sulfate, polysorbates, including, e.g., polysorbate 80, and mixtures of these components. Typically, the surfactant is present in the core in an amount of about 2 to about 7% w/w, and desirably, about 5% w/w of the core. In another embodiment, the surfactant is present in a ratio of about 5:3 drug: surfactant (e.g., pantoprazole sodium sesquihydrate to sodium lauryl sulfate) to about 10:1 drug: surfactant (e.g., pantoprazole sodium sesquihydrate to polysorbate 80). Advantageously, the surfactants in the multiparticulate formulation have been found to enhance the wettability and, thus, the speed and extent of release and absorption of the sodium pantoprazole, from the multi particulate formulation of the invention.

The spheroid core can further contain a disintegrant, a pH adjuster and, optionally a binder or another excipient such as hydroxypropyl methylcellulose (e.g., hypromellose 2208). Suitably, the total amount of disintegrant(s) present in the core is an amount of about 15% w/w to about 80% w/w, or about 20% w/w to about 70% w/w, or about 25% w/w to about 45% w/w, or about 30% w/w to about 42% w/w. In one embodiment, the total amount of drug to binder is represented by a ratio of from about 50:1 to about 40:1 by weight drug: binder. The total amount of a pH adjuster in the formulation can range from about 0.1% w/w to about 10% w/w of the multiparticulate, or about 1% w/w to about 8% w/w, or about 3% w/w to about 7% w/w. However, these percentages can be adjusted as needed or desired by one of skill in the art.

The disintegrant may be selected from among other known disintegrants, including, e.g., cellulose, and crospovidone, among others. In one embodiment, the disintegrant is selected from among microcrystalline cellulose and crospovidone, and mixtures thereof. The binder may be selected from among known binders, including e.g., cellulose, and povidone, among others. In one embodiment, the binder is hydroxylpropyl methyl cellulose (hypromellose). Suitable pH adjusters include, e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate, among others. Still other suitable components will be readily apparent to one of skill in the art.

In one embodiment, the spheroid core contains, w/w based on the dry uncoated core, about 45% pantoprazole sodium sesquihydrate (about 40% free pantoprazole), about 25 to 30%, and preferably about 27% microcrystalline cellulose, about 4 to 6%, and preferably about 5% polysorbate 80, about 14 to 16%, and preferably about 15% crospovidone, about 0.5 to 2%, and preferably about 1% hypromellose 2208, about 5 to 8%, and preferably about 6.5% sodium carbonate. In one embodiment, the spheroid core contains:

pantoprazole sodium sesquihydrate	45.24% w/w
microcrystalline cellulose	27.25% w/w
polysorbate 80	5% w/w
crospovidone	15% w/w
hypromellose 2208	1% w/w
sodium carbonate	6.5% w/w

In another embodiment, the spheroid core contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573

Although moisture is removed from the core during the drying process which is described below, the core preferably retains about 1% to about 2% w/w water. Without wishing to be bound by theory, the inventors believe that this water content contributes the stability of this multiparticulate as compared to the failed prior art attempts at forming a multiparticulate pantoprazole.

Optionally, an initial seal coat (or subcoat) can be applied directly to the core prior to coating with the enteric coat. Although the components of this seal coat can be modified by one of skill in the art, a particularly suitable initial seal coat is composed of hydroxypropyl methylcellulose (hypromellose) and water. For example, a suitable initial seal coat can be applied as a 7.5% w/w hypromellose solution. Typically, such a seal coat is in the range of about 2% w/w to about 4% w/w of the uncoated core or about 1% w/w to about 2% w/w of the coated multiparticulate.

In one embodiment, a multiparticulate with a subcoat contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
A. Sub Coat:	4.00 mg	1.943
Pantoprazole Sodium Pellets (40 mg pantoprazole per 100 mg pellets)	100.00 mg	48.573
Hydroxypropylmethyl cellulose 2910, USP, 6 cps	4.00 mg	1.943
Purified water, USP/BP/EP	9.33 mg*	
Total	104.00 mg	50.516

*removed during processing

The enteric coat is applied over the initial seal coat, if present, or directly to the uncoated spheroid core. Suitably, the enteric coat is applied such that it coats the core in an amount of about 15 to 45% w/w, or about 20% w/w to about

30% w/w, or about 25% w/w to 30% w/w of the multiparticulate. In one embodiment, the enteric coat is about 27.5 to 32.5% w/w of the multiparticulate. Suitably, the enteric coat contains a product which is a copolymer of methacrylic acid and methacrylates, such as the commercially available Eudragit L 30D-55. In one embodiment, the enteric coat is composed of a Eudragit L 30D-55 copolymer, talc, triethyl citrate, sodium hydroxide and water. More particularly, the enteric coating may contain about 30% w/w of multiparticulate (applied as a 30 wt % dispersion) of Eudragit L 30D-55 coating; about 15% w/w talc, about 3% triethyl citrate; a pH adjuster such as sodium hydroxide and water. Other suitable materials may be selected for use in the enteric coat including, e.g., hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and the like.

In one embodiment, a multiparticulate of the invention is provided with a subcoat over the core and an enteric coat as follows:

Ingredients	Amount/capsule	% w/w, based on total weight multiparticulate
Core + Subcoat	100.20 mg	48.67
Eudragit L30D-55	208.00 mg 62.40 (solids)	30.309
Talc, USP, Altalc 500 V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N solution	9.30 mg 0.36 (solids)	0.175
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	
Total	204.20 mg	99.186

*removed during processing

In one embodiment, the enteric-coated multiparticulate is further coated with a final seal coat. Suitably, this final seal coat is comprises hydroxypropyl methylcellulose, and about 0.1% w/w to 10% w/w of the coated multiparticle, 0.1% w/w to about 5% w/w, or about 0.2% w/w to about 4% w/w.

In one embodiment, a final seal coat of hydroxypropyl methylcellulose in an amount of 0.5 to 1% w/w of the multiparticulate in water (which is removed during processing) is applied over the enteric coat. Following this, a coating of talc can optionally be applied over the final seal coat, in an amount of about 0.05 w/w to about 1% w/w, and preferably 0.1% w/w to 0.5% w/w.

In one embodiment, the resulting multiparticulate formulation of the invention achieves a geometric mean AUC ratio of test/reference of 89 to 94 with a 90% confidence interval of 84 to 100 for the ratio or achieving a geometric mean Cmax ratio of test/reference of 62 to 66 with a 90% confidence interval of 56 to 74 for the ratio or an in-vitro dissolution profile as shown below:

		% Drug Release			
Media	Time	Initial	6 Months @ 25 C./ 60% RH	6 Months @ 40 C./ 75% RH	Target
Acid (pH 1.0)	2 hrs	0.33	0.45	0.6	NMT 10%
Followed by	3 min	—	0.91	0.85	—
Alkaline	6 min	—	3.61	1.83	
Buffer	9 min	—	52.25	16.45	—
(pH 6.8)	12 min	—	89.65	75.15	—
	15 min	101.58	97.15	91.92	—
	30 min	105.29	100.67	98.96	—
	45 min	105.29	100.57	99.14	NLT 75%
	60 min	105.06	100.52	99.07	—

In another embodiment, the resulting multiparticulate formulation of the invention achieves a mean AUC of 5451 to 5629 ng.h/ml and mean Cmax of 1865 to 1929 ng/ml or an in-vitro dissolution profile as shown below:

	% Drug Release*			
	Acid	Buffer (min)		
Batch	2 hrs	15	30	45
Initial	0.08	101.77	107.44	107.38
6 Months @40 C./75% RH	0.73	95.44	101.12	101.21
12 Months @25 C./60% RH	0.30	96.11	101.92	102.20

*Specifications: Acid at 2 hrs-NMT 10.0%; Buffer at 45 min-NLT 75%

However, the invention is not limited to these exemplary profiles.

Without wishing to be bound by theory, it is believed that final seal coat layer of hydroxypropyl methylcellulose provides a physical barrier for reduced contact between the mucoadhesive Eudragit layer and the upper GI tract, and thereby allows the reliable transit of the multiparticulates to the proper pH environment in the GI tract for effective release and absorption of the drug. In addition, the final seal coat layer of hydroxypropyl methylcellulose imparts anti-sticking properties to the multiparticulates and thus the multiparticulates are not sticking to the pouch material and/or nasogastric tube. The multiparticulates of the invention are useful for administration via the nasogastric tube and via food vehicles, particularly acidic food vehicles.

II. Method of Producing Multiparticulate Formulations of Invention

In another aspect, the invention provides a method of producing the multiparticulate formulations of the invention.

Typically, the uncoated pantoprazole compounds are prepared are follows. The dry components, including, at least the pantoprazole compound and the binder are dry blended in a suitable mixer under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for the selected equipment. Optionally, hydroxypropyl methylcellulose or crospovidone may be substituted or additionally included in this step. Additionally, a pH adjuster may be included in this step.

Subsequently, the liquid components, e.g., the surfactant and water, are mixed in to afford a granulated product by mixing under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for

the selected equipment. The granulation is then extruded and spheronized through a suitable device (e.g., a NICA extruder/spheronizer) and the resulting spheroids are dried, sifted, and optionally blended prior to storage.

The inventors have found that a significant advantage is provided to the stability of the compound when the multiparticulates of the invention are dried at low temperature. Desirably, the spheroid cores of the pantoprazole multiparticulates of the invention are dried to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%. As used herein, low temperature drying refers to a temperature not exceeding about 40° C. for a period of 10 to 12 hours. When the drying conditions exceed this temperature and time period, impurities are observed that contribute to instability. In one embodiment, drying of the core is performed in the range of 35° C. to 40° C., or about 37° C. to 39° C. for about 8 to 72 hours. In another embodiment, the core is dryed at about 40° C. for 10 to 12 hours. Suitably, when coating layers are applied as described, the drying temperature for the various coating layers is also in this range.

Optionally, an initial seal coat of a hydrophilic polymer can be applied to the uncoated multiparticulates. For example, an initial seal coat composed of hydroxypropyl methylcellulose and purified water can be applied on a fluid bed coater, e.g., by spraying.

The enteric coat can be applied directly to the uncoated spheroid core, i.e., the uncoated multiparticulate, or may be applied over an initial seal coat. The enteric coat as described above, is typically applied on a fluid bed wurster coater.

In one embodiment, a final seal coat is applied over the enteric coat and, optionally, talc is utilized in the final step prior to filling the multiparticulates into a suitable packaging unit.

The multiparticulate of the invention may be in any suitable form including, e.g., granules, pellets, beads, minitabs, spherules, beadlets, microcapsules, millispheres, nonocapsules, microspheres, platelets, tablets, and capsules, depending upon the desired route of delivery.

III. Formulations, Kits and Methods of Delivery

In another embodiment, the present invention provides products containing the pantoprazole multiparticulates of the invention.

Suitably, the multiparticulate compositions of the invention are formulated such that a patient receives a suitable amount of the pantoprazole, e.g., 5 mg to 200 mg, about 10 mg to about 100 mg, or about 40 mg (measured based upon free pantoprazole). Preferably, the formulations are such that a suitable dose is delivered in a single dosage unit. These doses may be administered daily for a suitable period of time, e.g., 4 weeks to 8 weeks, but can be delivered for a shorter period of time, e.g., 3 days to 3 weeks, one week to 3 months, or over a longer period, e.g., over 6 months, or longer. These compositions can be delivered alone or in combination with an antacid or other suitable composition.

In one embodiment, the invention provides a method of treating humans by administering an effective dose of the pantoprazole multiparticulates such that an area under curve (AUC) at least bioequivalent to Protonix® 40 mg tablet and Cmax as listed in Table VI are achieved.

In one embodiment, the pantoprazole multiparticulates are packaged for use by the patient or his caregiver. For example, the multiparticulates can be packaged in a foil or other suitable package and is suitable for mixing into a food product (e.g., applesauce and other acidic food vehicles) or into a drink for consumption by the patient.

The pantoprazole multiparticulate formulations of the invention are useful for treatment of gastroesophageal reflux disease (GERD), ulcers of the stomach and duodenum, and Zollinger-Ellison Syndrome.

In another embodiment, the pantoprazole multiparticulates are suspended in a physiologically compatible suspending liquid.

In yet another embodiment, the pantoprazole multiparticulates are filled in capsules, caplets or the like for oral delivery.

In still a further embodiment, the invention provides method of treating a subject in need thereof by administering an effective dose of the pantoprazole multiparticles of the invention.

The following examples illustrate specific embodiments of the invention and are not a limitation on the present invention.

EXAMPLE 1

Pantoprazole Sodium Multiparticulate Formulations

Using a NICA extruder/spheronizer, during initial formulation development, several prototypes of uncoated multiparticulates were manufactured to obtain a target immediate release profile similar to or faster than the pantoprazole sodium uncoated tablet, currently available as Protonix (20 mg and 40 mg) tablets. Levels of the disintegrant crospovidone from 5 to 28.5% and the binder hydroxypropyl methyl cellulose from 0.5 to 1% were evaluated during preparation of uncoated multiparticulates over four batches.

A. Preparation of Uncoated Pantoprazole Sodium Multiparticulates

More particularly, pantoprazole sodium sesquihydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (hypromellose 2208), crospovidone and sodium carbonate are dry blended in a Hobart mixer. Thereafter, polysorbate 80, NF (vegetable source) and purified water, USP, are added to the Hobart mixer. The resulting granulated produce is extruded and spheronized in a NICA® extruder/spheronizer and the spheroids are tray dried at a temperature not beyond 40° C. and sifted, followed by transfer to a PK blender. The final spheroids are stored in drums.

One of the batches (an approximately 200 gm batch) with 15% disintegrant crospovidone and with 1% hydroxypropyl methylcellulose (Hypromellose 2208)-was selected as a prototype with similar release profile. The sieve cut of the uncoated spheroids from this batch was between 500-1000 microns.

B. Prototype Lab Batch (Batch A)

Approximately 100 grams of these uncoated spheroids were coated in a 3" Wurster Fluid Bed coater with Eudragit L30D-55 and hypromellose to result in Enteric coated multiparticulates.

During coating for this batch, the level of hydroxypropyl methyl cellulose (HPMC) initial seal coat was 4% of the weight of the uncoated multiparticulates. The % w/w of the dry polymer Eudragit L30D-55 used was 22.16%. In the coating batch, talc was introduced as dry powder in the coating chamber instead of being a part of the suspension. This was due to the small nozzle size (0.5 mm) used for coating the 100 g batch, which could potentially be clogged. The percent of talc and triethyl citrate used for the lab batch was less as compared to the clinical batches which were subsequently prepared. The multiparticulates were hand filled into size #2 HPMC capsules at a fill weight of 206 mg. The capsules were tested in vitro in 0.11 N HCl and pH 6.8 phosphate buffer. Less than 1% was released in acid media in 2 hours and greater than 80% was released in basic media in 45 minutes as desired.

These capsules were tested in dogs. The C_{max} and AUC were 110 compared against the current marketed Protonix 20 mg tablet (and values were extrapolated to the 40 mg strength). It was seen that these multiparticulates released drug at a much faster rate than the current Protonix tablet in pH 6.8 phosphate buffer as desired. The final seal coat com-

prises hydroxypropyl methylcellulose (hypromellose) and water. This batch was packaged as spheroids in clear glass vials and placed on stability at accelerated conditions (30° C./65% relative humidity (RH) and 40° C./75% RH). The stability was monitored for 3 months. The potency and dissolution results are presented in Table I. The multiparticulates were stable over the three month period and a 40 mg equivalent dose of multiparticulates filled into capsules at each stability time point met all dissolution and stability criteria.

Dissolution was tested by filling the stored spheroids into capsule shells, and dissolving in 0.1 N HCl (target release at 2 hours: not more than (NMT) 10%), followed by dissolution in pH 6.8 phosphate buffer (target release at 45 min: not less than (NLT) 75%. The acceptance criteria further required a strength of 90 to 110% of the label claim.

TABLE I

Stability of multiparticulates in clear glass vials.

Test Unit	Time	Strength (HPLC) % Label	Dissolution-Percentage Released (avg) 0.1 N HCl	Secondary dissolution in phosphate buffer
Initial		100.0%	0.9%	91.6%
Ambient Room	1 month	97.2%	0.8%	88.5%
Temp	7 month	108.5%	0.8%	94.1%
30° C./60% RH	1 month	99.3%	0.5%	83.4%
	2 month	98.3%	NA	NA
	3 month	104.4%	0.7%	82.2%
40° C./75% RH	1 month	95.4%	0.7%	86.1[1]
	2 month	97.3%	NA	NA
	3 month	102.7%	0.7%	89.4%

[1]One capsule-78% released.

EXAMPLE 2

Coated Pantoprazole Sodium Multiparticulate Formulations (Batch B)

Based upon the lab batch A, a further scale-up batch of 1400 g was manufactured using a 7" wurster fluid bed coater. During coating for this batch, the level of hydroxypropyl methyl cellulose initial seal coat was 2% of the weight of the uncoated multiparticulates as compared to 4% for the coated Batch A. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. Also, the talc was added directly to the coating suspension as a larger nozzle size (1 mm) was used.

Initial release of coated multiparticulates in 0.1 N acid was high (9.0%) and very close to the limit of 10%. This Batch (B) did not meet the stability and dissolution criteria when tested at accelerated conditions (30° C./60% relative humidity (RH) and 40° C./75% RH). Trial from this batch indicated that an initial seal coat of greater than 2% of uncoated multiparticulates enhances stability of the multiparticulates. Additionally, more enteric polymer loading may be beneficial to control the release in acid media as the process is scaled up.

EXAMPLE 3

Preparation of Pantoprazole Multiparticulates Scale-Up Batch

A. Technical Batch

Using a NICA extruder/spheronizer, a 36 kg technical batch of uncoated multiparticulates was prepared and 20 kg of this batch were enteric coated in a Glatt GPCG-15 machine to result in a 32 kg batch of coated multiparticulates. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. This batch was filled into size #3 HPMC capsules at a fill weight of 156 mg. The release in 0.1 N HCl at 2 hours was greater than the desired 10%. Based on this, taking into account scale-up effects, minor adjustments were made to the formula and process for clinical batch.

B. Clinical Batch

Two 12 kg sub batches of a wet granulated mass were extruded and spheronized on a NICA extruder/spheronizer resulting in wet multiparticulates. The multiparticulates were tray dried at 40° C. for 10 to 12 hours to the desired % LOD of 3.4% to 4.3%. The batch was screened and only 16 kg of uncoated multiparticulates were used for coating to ensure uniformity and completeness of coating in the GPCG-15 machine. The sieved uncoated multiparticulates were coated with an initial hydroxypropyl methycellulose seal coat, followed by an Eudragit L30D-55 enteric coat, followed by a hydroxypropyl methycellulose final coat to result in 33 kg of coated multiparticulates. This batch was filled into size #2 HPMC capsules at a fill weight of 206 mg.

The release in 0.1 N HCl at 2 hours was less than the 10% limit and in pH 6.8 phosphate buffer, it was greater than the 80% limit at 45 minutes. The batch met in vitro release characteristics. The one month stability date showed that the multiparticulates were stable at 40° C./75% RH for one month. Currently, this batch is stable up to one year at room temperature and up to 6 months at 40 deg.C/75% RH. Stability study at room temperature condition beyond one year is ongoing. The one year room temperature stability results of this batch are shown in the following Table II.

The spheroid filled capsule had a faster in vitro release (dissolution) as compared to the Protonix 40 mg tablet in pH 6.8 phosphate buffer.

TABLE II

Stability of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg

Test	Appearance and Description	Strength (HPLC)	Water (KF)	Purity		Dissolution	
Specification	#2 Opaque white capsules (cap and body) containing white to off-white colored spheroids	90.0–110.0% Label Claim (LC)	For Information	Largest Single Known or Unknown Impurity ≤0.5 (RRT)	Total Known and Unknown Impurities ≤2.0	Dissolution in 0.1 N HCl NMT 10% in 2 hrs. Conforms to USP <724>	Dissolution in Phosphate Buffer NLT 75% in 45 min. Conforms to USP <724>
Unit		%	%	%	%	%	%
Initial	Conforms	100.3	5.1	BRL	BRL	0	105
Initial						0	107

TABLE II-continued

Stability of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg

Test	Appearance and Description	Strength (HPLC)	Water (KF)	Purity		Dissolution	
(Spheroids only)[a] 25° C./60% RH							
1 Month	No Change	99.5	5.2	0.17 (1.39)	0.17	1	103
2 Month	No Change	101.4	4.6	0.15 (1.38)[b]	0.23	0	101
3 Month	No Change	101.2	4.5	0.17 (1.39)	0.17	0	100
6 Month	No Change	101.3	4.5	0.18 (1.38)[b]	0.24	0	100
6 Month (Spheroids only)[a]						0	112
9 Months	No Change	99.2	5.1	0.21 (1.40)[b]	0.33	0	101
9 Months (Spheroids only)[a]						0	108
12 Months	No Change	99.1	5.1	0.08 (0.14)	0.23	0	102
12 Months (Spheroids only)[a]						0	104

BRL = Below Reporting Limit (0.05%).
NMT = Not more than.
NLT = Not less than.
RRT = Relative retention time.
[a]Initial and revalidation dissolution results are provided for Pantoprazole Sodium Spheroids, 40 mg/206 mg, which is the ingoing batch of spheroids used for manufacture of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg.
[b]Corresponds to the impurity at RRT = 1.39.

EXAMPLE 4
Evaluation of Batch A Formulation in Beagle Dogs

The in-vitro release data of the sodium pantoprazole multi particulate formulation shows a faster release than the current marketed tablet. This provides earlier absorption and thereby a faster onset of action. The dog data clearly shows earlier drug levels of sodium pantoprazole from multiparticulates as compared to the single monolithic tablets. Earlier onset of action provides faster relief from gastric pain and other gastrointestinal (GI) disorders.

Pantoprazole sodium formulations have been evaluated in Beagle Dogs (n=5). The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole is illustrated in the Table III below.

As illustrated, the non-optimized lab batch of sodium pantoprazole multiparticulate formulation dosed in dogs shows smaller lag time than the current marketed tablet. In the following table, AUC refers to the area under a curve plotting mean concentration against protocol time. C_{max} refers to the maximum observed concentration value in the blood sample after administration. T_{max} refers to the time point when C max occurs. T_{lag} refers to the time following administration before effective amounts of the drug are observed in the circulation; $t_{1/2}$ (hr) provides the half-life for drug elimination. Relative bioavailability compares the absorption of a product from the gut in comparison with a dose given intravenously (assumed 100%).

TABLE III

The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole

Parameter	20 mg Market Tablet Batch A Pantoprazole Na[a]	40 mg Multiparticulate Capsule Batch A with enteric coat - Pantoprazole Na
AUC (μg*hr/mL)	16.3 (2.46)	17.3 (2.33)
Cmax (μg/mL)	11.7 (3.55)	7.10 (1.76)
Tmax (hr)	1.70 (0.84)	1.20 (0.27)
tlag (hr)	1.10 (0.91)	0.25 (0.18)

TABLE III-continued

The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole

Parameter	20 mg Market Tablet Batch A Pantoprazole Na[a]	40 mg Multiparticulate Capsule Batch A with enteric coat - Pantoprazole Na
t ½ (hr)	0.62 (0.17)	0.77 (0.21)
Relative Bioavailability	—	AUC: 106%[b] Cmax: 61%[b]

[a]AUC and Cmax are normalized to a 40 mg dose
[b]Relative to Market Product Tablet

The dog data of the sodium pantoprazole multi particulate formulation gives a similar AUC as the current marketed tablet. Without wishing to be bound by theory, it is believed that the faster release and similar AUC of the multi particulates is achieved by lowering the level of the disintegrating agent crospovidone (as compared to the level in the tablet) and incorporating the functional excipient polysorbate 80 in the core of the spheroids.

EXAMPLE 5
Pantoprazole Sodium Sesquihydrate:Excipient Formulations

This study was performed to determine the compatibility of pantoprazole sodium sesquihydrate with hypromellose 2208, sodium lauryl sulfate (SLS), crospovidone, and polysorbate-80.

A. Study Design

The study consists of two sets of samples. The first set contained drug and excipient. The second set contained drug, excipient and approximately 2 μl water. The reason for the water along with the drug and the excipient is to see whether additional water present causes any incompatibility.

The excipients were mixed with the drug in the ratio indicated in the following table. The excipients and the drug were weighed into a glass vial. Then the vials were vortexed for 15 seconds. Similarly, a second set of samples was prepared. Approximately 2 μl (the smallest amount of water that can be added with the pipette in the lab) was added to these vials.

Then the vials were vortexed for 5 seconds. Finally, the first and second set of vials were capped and placed in stability chambers. The conditions tested were 40°/75% RH and 51° C. for 3 weeks.

B. Results

The results of this drug-excipient compatibility study are presented as % recovery in the Table IV below. The selection criteria for the compatibility or in-compatibility are based on the % recovery between 90-110%.

TABLE IV

Drug: Excipient Compatibility Results

Excipient	Ratio of Drug:Excipient	% Recovery: Drug + Excipient, 40° C./75% RH 3 weeks	% Recovery: Drug + Excipient, 51° C. 3 weeks	% Recovery: Drug + Excipient + Water, 40° C./75% RH 3 weeks	% Recovery: Drug + Excipient + Water, 51° C. 3 weeks
Control (Drug alone)	—	94.67	100.53	94.60	96.64
Hypromellose 2208, USP, 3 cps	10:1	99.209	93.248	93.811	97.421
Sodium Lauryl Sulfate (SLS)	5:3	99.947	98.763	95.466	95.088
Crospovidone, NF	10:1	100.080	98.908	97.201	105.716
Polysorbate-80, NF BP/EP (vegetable source)	10:1	98.301	90.961	99.908	81.405

From the results shown in the table, the following conclusions can be drawn. Hypermellose 2208, SLS, crospovidone and polysorbate-80 are compatible with pantoprazole sodium sequihydrate at 40° C./75% RH for 3 weeks. Hypromellose 2208, SLS and crospovidone are compatible with pantoprazole sodium sequihydrate at 40° C./75% RH and 51° C. with and without additional water for 3 weeks.

In this study degradation compounds were not studied. However, the pediatric clinical formulation, [pantoprazole sodium sesquihydrate 45.24% w/w; microcrystalline cellulose 27.25% w/w; polysorbate 80 5% w/w; crospovidone 15% w/w; hypromellose 2208 1% w/w; sodium carbonate 6.5% w/w; purified water q.s.], was studied under accelerated conditions of 40° C./75% RH and is stable up to 6 months, providing a 2 year room temperature shelf life.

The components of the pediatric formulation are provided in the following Table V.

Formulation: Ingredients	Multiparticulates: Amount/ Capsule	Multiparticulates: % w/w
Core:		
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286

-continued

Formulation: Ingredients	Multiparticulates: Amount/ Capsule	Multiparticulates: % w/w
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573
Enteric Coat:	100.20 mg	48.67
Eudragit L30D-55	208.00 mg 62.40 (solids)	30.309
Talc, USP, Altalc 500V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N solution	9.30 mg 0.36 (solids)	0.175
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	
Total	204.20 mg	99.186
Final Seal Coat:	1.54 mg	0.748
Hydroxypropyl Methylcellulose, USP 2910, 6 cps	1.54 mg	0.748
Purified water, USP/BP/EP	18.99 mg*	
Total	205.74 mg	99.934
Talc, USP, Altalc 500V	0.14 mg	0.068
Total	205.88 mg	100.002

*removed during processing

EXAMPLE 6

Evaluation of Pantoprazole Sodium Formulation in Human Adult Subjects

In this study, 40 mg pantoprazole sodium, formulated as described, clinical pediatric formulation, was administered to

healthy human adults (n=24) by sprinkling in applesauce, in tablet form, or as an aqueous suspension prepared using an inactive powder blend and water (8 in each group).

In the following Table VI, column 1 provides the pharmacokinetic (PK) parameters, AUC (area under the concentration curve), AUC_T is the area under the concentration time curve, and C_{max}, maximum concentration. The second column provides the test/reference geometric mean (GM) ratio. The third column provides the confidence interval for the GM ratio. [The FDA considers a test product to be bioequivalent to a reference product if the 90% confidence interval (CI) of the geometric mean ratio of AUC and C_{max} between the test and reference fall within 80-125%].—The confidence interval is calculated using WinNonlin software.

TABLE VI

Human PK study Results

PK parameter	Test/Reference GM ratio	90% CI for ratio*
A. Spheroids sprinkled in applesauce:		
AUC	90	84-96
AUC_T	89	84-95
Cmax	62	56-70
B. Spheroids in suspension:		
AUC	94	88-100
AUC_T	94	88-100
Cmax	66	60-74

The lag time in the absorption of the tablet was higher compared to the sprinkle and suspension formulations. The entire drug in the tablet is released over a small time interval and therefore a higher C_{max} is obtained. With the spheroid formulations, drug from each spheroid is released over a longer time interval and therefore the C_{max} is lower than the tablet. However, the period of time following administration that pantoprazole remained in the circulation is similar for the 3 formulations.

All documents identified herein are incorporated by reference. One of skill in the art will recognize that minor modifications to the conditions and techniques described in the specific embodiments described herein can be varied without departing from the present invention. Such minor modification and variants are within the scope of the invention as defined by the following claims.

The invention claimed is:

1. A method of producing a multiparticulate formulation of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, said method comprising the steps of:

producing a spheroid core comprising about 45% w/w pantoprazole sodium sesquihydrate, as a sole active component in the multiparticulate formulation and about 25% to 30% w/w microcrystalline cellulose, about 4% to 6% w/w polysorbate 80, about 14% to 16% w/w crospovidone, about 0.5 to 2% w/w hydroxypropyl methylcellulose, and about 5% to 8% w/w sodium carbonate a surfactant via extrusion and spheronization, said core further containing about 1 to about 2% w/w water;

applying an initial seal coat comprising hydroxypropyl methylcellulose to the spheroid core,

applying an enteric coating to the initial seal coated spheroid core, said enteric coating comprising a copolymer of methacrylic acid and methacrylates;

and optionally applying a final seal coat to the enteric-coated spheroid core, said final seal coat being about 1 wt % of the multiparticulate;

wherein the multiparticulates have an average diameter of about 0.7 mm to about 1.25 mm.

2. The method according to claim 1, wherein the spheroid core is prepared by mixing the ingredients in a low shear mixer at low shear conditions at a range of about 25 rpm to 35 rpm.

3. The method according to claim 2, wherein the low shear conditions are 32 rpm.

4. The method according to claim 2, wherein the spheroid cores are dried at a low temperature not exceeding about 40° C. for a period of 8 to 72 hours to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%.

5. The method according to claim 1, further comprising the step of applying a layer of talc in an amount of 0.05% w/w to 0.1% w/w of the multiparticulates.

6. The method according to claim 1, wherein the enteric coating is sprayed as a suspension onto the spheroid core.

7. Pantoprazole multiparticulates having reduced release under gastric conditions and fast release at neutral pH, wherein each of said multiparticulates comprises: a spheroid core comprising about 45% w/w pantoprazole sodium sesquihydrate as a sole active component in the multiparticulates about 25% to 30% w/w microcrystalline cellulose, about 4% to 6% w/w polysorbate 80, about 14% to 16% w/w crospovidone, about 0.5 to 2% w/w hydroxypropyl methylcellulose, about 5% to 8% w/w sodium carbonate, and about 1 to 2% w/w water; an initial seal coat comprising hydroxypropyl methylcellulose on the spheroid core; and an enteric coat on the initial seal coat, wherein said multiparticulates have an average diameter of about 0.7 mm to about 1.25 mm.

8. The multiparticulates according to claim 7, wherein said multiparticulates have an average diameter of about 1 mm.

9. The multiparticulates according to claim 7, wherein said enteric coat comprises about 48% w/w of the particulate,

10. The multiparticulates according to claim 7, further comprising a final seal coat on the enteric coat.

11. The multiparticulates according to claim 10, wherein the final seal coat comprises about 0.1 to 10 wt % of the multiparticulates.

12. The multiparticulates according to claim 10, wherein the final seal coat comprises hydroxypropyl methylcellulose (hypromellose).

13. The multiparticulates according to claim 7 wherein said initial seal coat is in the range of about 2 to about 4% w/w of the weight of the uncoated core.

14. The multiparticulates according to claim 7, wherein the enteric coating comprises about 30% w/w of methacrylic acid and methyacrylate copolymer, about 15% w/w talc, about 3% triethyl citrate and a pH adjuster; said amounts being by weight of the multiparticulates.

15. A pantoprazole formulation comprising a suspension comprising the multiparticulates of claim 7 and a physiologically compatible suspending liquid.

16. A capsule comprising the multiparticulates of claim 7.

17. A foil packet comprising the multiparticulates according to claim 7.

18. The method according to claim 1, wherein the spheroid core consists essentially of:

pantoprazole sodium sesquihydrate	about 45% w/w
microcrystalline cellulose	about 27% w/w
polysorbate 80	about 5% w/w
crospovidone	about 15% w/w
hydroxypropylmethylcellulose	about 1% w/w
sodium carbonate	about 6.5% w/w; and
water.	

19. The pantoprazole multiparticulates according to claim 7, wherein the spheroid core consists essentially of:

pantoprazole sodium sesquihydrate	about 45% w/w
microcrystalline cellulose	about 27% w/w
polysorbate 80	about 5% w/w
crospovidone	about 15% w/w
hydroxypropylmethylcellulose	about 1% w/w
sodium carbonate	about 6.5% w/w; and
water.	

20. A plurality of pantoprazole multiparticulates, each comprising: a spheroid core consisting essentially of about 45% w/w pantoprazole sodium sesquihydrate, about 27% w/w microcrystalline cellulose, about 5% w/w polysorbate 80; about 15% w/w crospovidone; about 1% w/w hydroxypropy methylcellulose, about 6.5% w/w sodium carbonate; and water; an inner seal coat comprising hydroxypropyl methylcellulose; and an enteric coating comprising a methacrylic acid and meth[yl]acrylate polymer, and triethylcitrate, wherein multiparticulates have an average diameter in the range of about 0.7 mm to about 1.25 mm.

21. The product according to claim 20, wherein the enteric coating further comprises talc.

22. The product according to claim 21, wherein the enteric coating further comprises sodium hydroxide.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,544,370 B2
APPLICATION NO. : 10/955567
DATED : June 9, 2009
INVENTOR(S) : Sripriya Rao et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title Page, Item [75] Inventors: Hanumantharao Tatapudy, Suffern, NJ, replace with -- Hanumantharao Tatapudy, Suffern, NY --;

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,544,370 B2
APPLICATION NO. : 10/955567
DATED : June 9, 2009
INVENTOR(S) : Rao et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by (495) days

Delete the phrase "by 495 days" and insert -- by 615 days --

Signed and Sealed this

Nineteenth Day of January, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office



(12) **United States Patent**
Venkata Ramana Rao et al.

(10) **Patent No.: US 7,550,153 B2**
(45) **Date of Patent: *Jun. 23, 2009**

(54) **PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS**

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

This patent is subject to a terminal disclaimer.

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(51) **Int. Cl.**
A61K 9/64 (2006.01)

(52) **U.S. Cl.** **424/456**

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Assistant Examiner—Bethany Barham
(74) *Attorney, Agent, or Firm*—Paul Carango, Esquire; Howson & Howson LLP

(57) **ABSTRACT**

Pantoprazole sodium multiparticulates are described which avoid sticking to nasogastric and gastronomy tubes. The pantoprazole multiparticulates have a spheroid core of pantoprazole or an enantiomer thereof, or a salt thereof, a surfactant, and a disintegrant; a sub coat which is comprised of hydroxypropyl methylcellulose(hypromellose) and water, an enteric coat on the sub-coat, and a final seal coat over the enteric coat, which is composed of hydroxypropyl methylcellulose (hypromellose) and water.

21 Claims, No Drawings

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PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation of U.S. patent application Ser. No. 10/955,567, filed Sep. 30, 2004, which claims the benefit under 35 USC 119(e) of prior U.S. Provisional Patent Application No. 60/507,810, filed Oct. 1, 2003.

BACKGROUND OF THE INVENTION

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole, is a H+/K+-adenosine triphosphate (ATP) inhibitor (also known as acid pump or proton pump inhibitor (PPI), is an enzyme present in the gastric parietal cells. It is believed that these drugs are metabolized in the parietal cells to active sulfenamide metabolites that inactivate the sulfhydryl group of the proton pump, thus reducing the hydrogen ion secretion. PPIs are generally lipophilic weak bases with poor aqueous solubility at low pH. Many PPIs are unstable in low pH solutions and undergo rapid acid-catalyzed degradation, and they are relatively stable at neutral or high pH.

The current commercial oral formulations of sodium pantoprazole are single unit coated tablets. See, e.g., U.S. Pat. No. 5,997,903, which describes oral forms of pantoprazole that consist of a core, an intermediate layer and an outer layer. The current coating has a tendency to cause undesirable sticking of the tablet to the gastrointestinal tract.

Multiparticulate formulations, because of their nature of dispersing in the gastrointestinal tract, show a reduced food effect and variability in gastric emptying times, thereby providing for reduced inter and intra subject variability, as compared to single unit tablets (Intl. Journal of Pharmaceutics 140 [1996] 229-235).

Several unsuccessful attempts have been made in the past to develop a multiparticulate formulation of pantoprazole. However, these attempts yielded multiparticulates that were not bioequivalent to tablets, only 70% relative bioavailability was found. Another attempt using different technologies-non-pareil seed coating and extrusion/spheronization, resulted in a product that did not provide the appropriate release in acid conditions. In addition, these attempts yielded product that was unstable, as observed by discoloration, when stored at room temperature.

SUMMARY OF THE INVENTION

The invention provides a stable multiparticulate pantoprazole formulation that provides reduced inter and intra subject variability.

In one embodiment, the pantoprazole multiparticulates of the invention is composed of a spheroid core comprising pantoprazole or an enantiomer thereof, or a salt or hydrate thereof, at least one surfactant, at least one disintegrant, and about 1% to about 2% w/w water; an enteric coat on the core, said enteric coat comprising a copolymer of methacrylic acid and methacrylates in the range of about 15 to about 45% w/w of the spheroid core; wherein said multiparticulates have an average size of about 1 mm in diameter.

Advantageously, the multiparticulate formulations of the invention are stable under room temperature storage conditions for at least twelve months. Based on the trend analysis using the twelve month room temperature data and 6 month 40° C./75% relative humidity (RH) data available to date, the multiparticulates of the invention should have a shelf life of over 2 years. Typically, a multiparticulate formulation of the invention is considered stable if it retains 90% to 110% of its potency during shelf life storage.

This pantoprazole multiparticulate formulation of the invention is less prone to adherence to the intestinal walls, nasogastric and gastromy tubes, and pouch material thereby giving predictable delivery of the drug product to the site of drug release. It also provides for an early onset of action for relief of gastrointestinal pain and has a prolonged duration of action. This formulation allows dosing to pediatric patients and patients who have difficulty swallowing solid foods. This formulation also allows for drug delivery via nasogastric and gastrostomy tubes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a multiparticulate formulation of pantoprazole having a unique combination of excipients and a surfactant (e.g., polysorbate 80) that are compatible with pantoprazole sodium in the presence of an alkaline pH environment. Further, the invention provides a process that utilizes low shear during granulation and low temperature during drying for preparation of the multiparticulate. This process contributes to the stability of the core of the multiparticulates of the invention.

In one aspect, the invention provides multiparticulate formulations of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, i.e., in the lower gastrointestinal tract.

The multi particulate formulation of sodium pantoprazole of the invention provides an enhanced system for the delivery of pantoprazole to patients. The current marketed formulation is a single monolithic tablet. The present formulation of multiparticulate spheroids, which is adaptable for use in a capsule or a foil packet, can be prepared by extrusion/spheronization plus coating technology.

The composition of the multiparticulate of the invention, and the enteric coat, e.g., Eudragit, allows for reduced release at low pH (~1) and fast release at a neutral pH (~7). This provides faster blood levels of the drug, in patients, and thereby a faster onset of action. The smaller T_{lag} value of multiparticulate formulation as compared to that of a single monolithic tablet based on the results from dog data indicates faster onset of action of multiparticulate formulation.

The use of a multi particulate formulation facilitates dosing to pediatric patients and patients who have trouble swallowing, by dispersing the spheroids in a suspending liquid or sprinkling/dispersing in a low pH liquid like applesauce, prior to administration. The suspending liquid could be made prior to administration by mixing a blend of powder material with water. The smaller size of the multi particulates, in a capsule or pouch or any other container, also allows dosing through nasogastric or gastrostomy tube.

This formulation allows for a faster relief of GI pain, and prolonged duration of action (extended release), as compared to the current marketed tablet.

I. Multiparticulates of the Invention

Suitably, the multiparticulates are in the range of about 0.1 to 2 mm, or 0.5 mm to 1.5 mm, or 0.7 mm to 1.25 mm, or 0.8 mm to 1 mm. In one embodiment, the multiparticulates in a composition of the invention average about 1 mm in diameter. Typically, the multiparticulates of the invention are no greater than about 1 mm in size in order to facilitate passage through nasogastric tubes

The multiparticulates of the invention are composed, at a minimum, of a spheroid core with an enteric coat over the core. In between the core and enteric coat an initial seal coat may be applied, e.g., comprising a coating of hydroxylpropyl methylcellulose(hypromellose). Also, over the enteric coat a final seal coat may be applied, e.g., a coating of hydroxylpropyl methyl cellulose(hypromellose). The spheroid core is composed of, at a minimum, a pantoprazole or a salt thereof, and a surfactant.

As used herein unless the context requires otherwise, the term 'pantoprazole' refers to 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole and enantiomers thereof and the term 'pantoprazole compound' includes pantoprazole and enantiomers and salts and hydrates thereof. The active compound, pantoprazole is described in European Patent 166 287, which describes the preparation thereof, and is available commercially under the brand name PROTONIX®. Examples of pharmaceutically acceptable salts of pantoprazole include, e.g., sodium, magnesium, and calcium, among others; still others are described in the European Patent 166 286, which is incorporated by reference herein. The selection of a suitable salt is not a limitation of the invention. In one embodiment, the salt is sodium. Typically, the pantoprazole compound is present in the range of from about 5 to 50% w/w, more preferably about 20 to 45% w/w, of the total multiparticulate.

Suitable surfactants are known to those of skill in the art. However, particularly desirable are sodium lauryl sulfate, polysorbates, including, e.g., polysorbate 80, and mixtures of these components. Typically, the surfactant is present in the core in an amount of about 2 to about 7% w/w, and desirably, about 5% w/w of the core. In another embodiment, the surfactant is present in a ratio of about 5:3 drug: surfactant (e.g., pantoprazole sodium sesquihydrate to sodium lauryl sulfate) to about 10:1 drug: surfactant (e.g., pantoprazole sodium sesquihydrate to polysorbate 80). Advantageously, the surfactants in the multiparticulate formulation have been found to enhance the wettability and, thus, the speed and extent of release and absorption of the sodium pantoprazole, from the multi particulate formulation of the invention.

The spheroid core can further contain a disintegrant, a pH adjuster and, optionally a binder or another excipient such as hydroxypropyl methylcellulose (e.g., hypromellose 2208). Suitably, the total amount of disintegrant(s) present in the core is an amount of about 15% w/w to about 80% w/w, or about 20% w/w to about 70% w/w, or about 25% w/w to about 45% w/w, or about 30% w/w to about 42% w/w. In one embodiment, the total amount of drug to binder is represented by a ratio of from about 50:1 to about 40:1 by weight drug: binder. The total amount of a pH adjuster in the formulation can range from about 0.1% w/w to about 10% w/w of the multiparticulate, or about 1% w/w to about 8% w/w, or about 3% w/w to about 7% w/w. However, these percentages can be adjusted as needed or desired by one of skill in the art.

The disintegrant may be selected from among other known disintegrants, including, e.g., cellulose, and crospovidone, among others. In one embodiment, the disintegrant is selected from among microcrystalline cellulose and crospovidone, and mixtures thereof. The binder may be selected from among known binders, including e.g., cellulose, and povidone, among others. In one embodiment, the binder is hydroxylpropyl methyl cellulose(hypromellose). Suitable pH adjusters include, e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate, among others. Still other suitable components will be readily apparent to one of skill in the art.

In one embodiment, the spheroid core contains, w/w based on the dry uncoated core, about 45% pantoprazole sodium sesquihydrate (about 40% free pantoprazole), about 25 to 30%, and preferably about 27% microcrystalline cellulose, about 4 to 6%, and preferably about 5% polysorbate 80, about 14 to 16%, and preferably about 15% crospovidone, about 0.5 to 2%, and preferably about 1% hypromellose 2208, about 5 to 8%, and preferably about 6.5% sodium carbonate. In one embodiment, the spheroid core contains:

pantoprazole sodium sesquihydrate	45.24% w/w
microcrystalline cellulose	27.25% w/w
polysorbate 80	5% w/w
crospovidone	15% w/w
hypromellose 2208	1% w/w
sodium carbonate	6.5% w/w

In another embodiment, the spheroid core contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573

Although moisture is removed from the core during the drying process which is described below, the core preferably retains about 1% to about 2% w/w water. Without wishing to be bound by theory, the inventors believe that this water content contributes the stability of this multiparticulate as compared to the failed prior art attempts at forming a multiparticulate pantoprazole.

Optionally, an initial seal coat (or subcoat) can be applied directly to the core prior to coating with the enteric coat. Although the components of this seal coat can be modified by one of skill in the art, a particularly suitable initial seal coat is composed of hydroxypropyl methylcellulose(hypromellose) and water. For example, a suitable initial seal coat can be applied as a 7.5% w/w hypromellose solution. Typically, such a seal coat is in the range of about 2% w/w to about 4% w/w of the uncoated core or about 1% w/w to about 2% w/w of the coated multiparticulate.

In one embodiment, a multiparticulate with a subcoat contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
A. Sub Coat:	4.00 mg	1.943
Pantoprazole Sodium Pellets (40 mg pantoprazole per 100 mg pellets)	100.00 mg	48.573

-continued

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
Hydroxypropylmethyl cellulose 2910, USP, 6 cps	4.00 mg	1.943
Purified water, USP/BP/EP	9.33 mg*	
Total	104.00 mg	50.516

*removed during processing

The enteric coat is applied over the initial seal coat, if present, or directly to the uncoated spheroid core. Suitably, the enteric coat is applied such that it coats the core in an amount of about 15 to 45% w/w, or about 20% w/w to about 30% w/w, or about 25% w/w to 30% w/w of the multiparticulate. In one embodiment, the enteric coat is about 27.5 to 32.5% w/w of the multiparticulate. Suitably, the enteric coat contains a product which is a copolymer of methacrylic acid and methacrylates, such as the commercially available Eudragit L 30D-55. In one embodiment, the enteric coat is composed of a Eudragit L30D-55 copolymer, talc, triethyl citrate, sodium hydroxide and water. More particularly, the enteric coating may contain about 30% w/w of multiparticulate (applied as a 30 wt % dispersion) of Eudragit L 30D-55 coating; about 15% w/w talc, about 3% triethyl citrate; a pH adjuster such as sodium hydroxide and water. Other suitable materials may be selected for use in the enteric coat including, e.g., hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and the like.

In one embodiment, a multiparticulate of the invention is provided with a subcoat over the core and an enteric coat as follows:

Ingredients	Amount/capsule	% w/w, based on total weight multiparticulate
Core + Subcoat	100.20 mg	48.67
Eudragit L30D-55	208.00 mg 62.40 (solids)	30.309
Talc, USP, Altalc 500V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N solution	9.30 mg 0.36 (solids)	0.175
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	
Total	204.20 mg	99.186

*removed during processing

In one embodiment, the enteric-coated multiparticulate is further coated with a final seal coat. Suitably, this final seal coat is comprises hydroxypropyl methylcellulose, and about 0.1% w/w to 10% w/w of the coated multiparticulate, 0.1% w/w to about 5% w/w, or about 0.2% w/w to about 4% w/w.

In one embodiment, a final seal coat of hydroxypropyl methylcellulose in an amount of 0.5 to 1% w/w of the multiparticulate in water (which is removed during processing) is applied over the enteric coat. Following this, a coating of talc can optionally be applied over the final seal coat, in an amount of about 0.05 w/w to about 1% w/w, and preferably 0.1% w/w to 0.5% w/w.

In one embodiment, the resulting multiparticulate formulation of the invention achieves a geometric mean AUC ratio of test/reference of 89 to 94 with a 90% confidence interval of 84 to 100 for the ratio or achieving a geometric mean Cmax ratio of test/reference of 62 to 66 with a 90% confidence interval of 56 to 74 for the ratio or an in-vitro dissolution profile as shown below:

		% Drug Release			
Media	Time	Initial	6 Months @ 25 C./ 60% RH	6 Months @ 40 C./ 75% RH	Target
Acid (pH 1.0)	2 hrs	0.33	0.45	0.6	NMT 10%
Followed by	3 min	—	0.91	0.85	—
Alkaline	6 min	—	3.61	1.83	—
Buffer	9 min	—	52.25	16.45	—
(pH 6.8)	12 min	—	89.65	75.15	—
	15 min	101.58	97.15	91.92	—
	30 min	105.29	100.67	98.96	—
	45 min	105.29	100.57	99.14	NLT 75%
	60 min	105.06	100.52	99.07	—

In another embodiment, the resulting multiparticulate formulation of the invention achieves a mean AUC of 5451 to 5629 ng.h/ml and mean Cmax of 1865 to 1929 ng/ml or an in-vitro dissolution profile as shown below:

	% Drug Release*			
	Acid	Buffer (min)		
Batch	2 hrs	15	30	45
Initial	0.08	101.77	107.44	107.38
6 Months @40 C./75% RH	0.73	95.44	101.12	101.21
12 Months @25 C./60% RH	0.30	96.11	101.92	102.20

*Specifications: Acid at 2 hrs- NMT 10.0%; Buffer at 45 min- NLT 75%

However, the invention is not limited to these exemplary profiles.

Without wishing to be bound by theory, it is believed that final seal coat layer of hydroxypropyl methylcellulose provides a physical barrier for reduced contact between the mucoadhesive Eudragit layer and the upper GI tract, and thereby allows the reliable transit of the multiparticulates to the proper pH environment in the GI tract for effective release and absorption of the drug. In addition, the final seal coat layer of hydroxypropyl methylcellulose imparts anti-sticking properties to the multiparticulates and thus the multiparticulates are not sticking to the pouch material and/or nasogastric tube. The multiparticulates of the invention are useful for administration via the nasogastric tube and via food vehicles, particularly acidic food vehicles.

II. Method of Producing Multiparticulate Formulations of Invention

In another aspect, the invention provides a method of producing the multiparticulate formulations of the invention.

Typically, the uncoated pantoprazole compounds are prepared are follows. The dry components, including, at least the pantoprazole compound and the binder are dry blended in a suitable mixer under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for

the selected equipment. Optionally, hydroxypropyl methylcellulose or crospovidone may be substituted or additionally included in this step. Additionally, a pH adjuster may be included in this step.

Subsequently, the liquid components, e.g., the surfactant and water, are mixed in to afford a granulated product by mixing under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for the selected equipment. The granulation is then extruded and spheronized through a suitable device (e.g., a NICA extruder/spheronizer) and the resulting spheroids are dried, sifted, and optionally blended prior to storage.

The inventors have found that a significant advantage is provided to the stability of the compound when the multiparticulates of the invention are dried at low temperature. Desirably, the spheroid cores of the pantoprazole multiparticulates of the invention are dried to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%. As used herein, low temperature drying refers to a temperature not exceeding about 40° C. for a period of 10 to 12 hours. When the drying conditions exceed this temperature and time period, impurities are observed that contribute to instability. In one embodiment, drying of the core is performed in the range of 35° C. to 40° C., or about 37° C. to 39° C. for about 8 to 72 hours. In another embodiment, the core is dryed at about 40° C. for 10 to 12 hours. Suitably, when coating layers are applied as described, the drying temperature for the various coating layers is also in this range.

Optionally, an initial seal coat of a hydrophilic polymer can be applied to the uncoated multiparticulates. For example, an initial seal coat composed of hydroxypropyl methylcellulose and purified water can be applied on a fluid bed coater, e.g., by spraying.

The enteric coat can be applied directly to the uncoated spheroid core, i.e., the uncoated multiparticulate, or may be applied over an initial seal coat. The enteric coat as described above, is typically applied on a fluid bed wurster coater.

In one embodiment, a final seal coat is applied over the enteric coat and, optionally, talc is utilized in the final step prior to filling the multiparticulates into a suitable packaging unit.

The multiparticulate of the invention may be in any suitable form including, e.g., granules, pellets, beads, minitabs, spherules, beadlets, microcapsules, millispheres, nanocapsules, microspheres, platelets, tablets, and capsules, depending upon the desired route of delivery.

III. Formulations, Kits and Methods of Delivery

In another embodiment, the present invention provides products containing the pantoprazole multiparticulates of the invention.

Suitably, the multiparticulate compositions of the invention are formulated such that a patient receives a suitable amount of the pantoprazole, e.g., 5 mg to 200 mg, about 10 mg to about 100 mg, or about 40 mg (measured based upon free pantoprazole). Preferably, the formulations are such that a suitable dose is delivered in a single dosage unit. These doses may be administered daily for a suitable period of time, e.g., 4 weeks to 8 weeks, but can be delivered for a shorter period of time, e.g., 3 days to 3 weeks, one week to 3 months, or over a longer period, e.g., over 6 months, or longer. These compositions can be delivered alone or in combination with an antacid or other suitable composition.

In one embodiment, the invention provides a method of treating humans by administering an effective dose of the pantoprazole multiparticulates such that an area under curve (AUC) at least bioequivalent to Protonix® 40 mg tablet and Cmax as listed in Table VI are achieved.

In one embodiment, the pantoprazole multiparticulates are packaged for use by the patient or his caregiver. For example, the multiparticulates can be packaged in a foil or other suitable package and is suitable for mixing into a food product (e.g., applesauce and other acidic food vehicles) or into a drink for consumption by the patient.

The pantoprazole multiparticulate formulations of the invention are useful for treatment of gastroesophageal reflux disease (GERD), ulcers of the stomach and duodenum, and Zollinger-Ellison Syndrome.

In another embodiment, the pantoprazole multiparticulates are suspended in a physiologically compatible suspending liquid.

In yet another embodiment, the pantoprazole multiparticulates are filled in capsules, caplets or the like for oral delivery.

In still a further embodiment, the invention provides method of treating a subject in need thereof by administering an effective dose of the pantoprazole multiparticles of the invention.

The following examples illustrate specific embodiments of the invention and are not a limitation on the present invention.

EXAMPLE 1

Pantoprazole Sodium Multiparticulate Formulations

Using a NICA extruder/spheronizer, during initial formulation development, several prototypes of uncoated multiparticulates were manufactured to obtain a target immediate release profile similar to or faster than the pantoprazole sodium uncoated tablet, currently available as Protonix (20 mg and 40 mg) tablets. Levels of the disintegrant crospovidone from 5 to 28.5% and the binder hydroxypropyl methyl cellulose from 0.5 to 1% were evaluated during preparation of uncoated multiparticulates over four batches.

A. Preparation of Uncoated Pantoprazole Sodium Multiparticulates

More particularly, pantoprazole sodium sesquihydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (hypromellose 2208), crospovidone and sodium carbonate are dry blended in a Hobart mixer. Thereafter, polysorbate 80, NF (vegetable source) and purified water, USP, are added to the Hobart mixer. The resulting granulated produce is extruded and spheronized in a NICA® extruder/spheronizer and the spheroids are tray dried at a temperature not beyond 40° C. and sifted, followed by transfer to a PK blender. The final spheroids are stored in drums.

One of the batches (an approximately 200 gm batch) with 15% disintegrant crospovidone and with 1% hydroxypropyl methylcellulose (Hypromellose 2208)-was selected as a prototype with similar release profile. The sieve cut of the uncoated spheroids from this batch was between 500-1000 microns.

B. Prototype Lab Batch (Batch A)

Approximately 100 grams of these uncoated spheroids were coated in a 3" Wurster Fluid Bed coater with Eudragit L30D-55 and hypromellose to result in Enteric coated multiparticulates.

During coating for this batch, the level of hydroxypropyl methyl cellulose (HPMC) initial seal coat was 4% of the weight of the uncoated multiparticulates. The % w/w of the dry polymer Eudragit L30D-55 used was 22.16%. In the coating batch, talc was introduced as dry powder in the coating chamber instead of being a part of the suspension. This was due to the small nozzle size (0.5 mm) used for coating the 100 g batch, which could potentially be clogged. The percent of talc and triethyl citrate used for the lab batch was less as compared to the clinical batches which were subsequently prepared. The multiparticulates were hand filled into size #2 HPMC capsules at a fill weight of 206 mg. The capsules were tested in vitro in 0.1 N HCl and pH 6.8 phosphate buffer. Less than 1% was released in acid media in 2 hours and greater than 80% was released in basic media in 45 minutes as desired.

These capsules were tested in dogs. The C_{max} and AUC were compared against the current marketed Protonix 20 mg tablet (and values were extrapolated to the 40 mg strength). It was seen that these multiparticulates released drug at a much faster rate than the current Protonix tablet in pH 6.8 phosphate buffer as desired. The final seal coat comprises hydroxypropyl methylcellulose (hypromellose) and water. This batch was packaged as spheroids in clear glass vials and placed on stability at accelerated conditions (30° C./65% relative humidity (RH) and 40° C./75% RH). The stability was monitored for 3 months. The potency and dissolution results are presented in Table I. The multiparticulates were stable over the three month period and a 40 mg equivalent dose of multiparticulates filled into capsules at each stability time point met all dissolution and stability criteria Dissolution was tested by filling the stored spheroids into capsule shells, and dissolving in 0.1 N HCl (target release at 2 hours: not more than (NMT) 10%), followed by dissolution in pH 6.8 phosphate buffer (target release at 45 min: not less than (NLT) 75%. The acceptance criteria further required a strength of 90 to 110% of the label claim.

TABLE I

Stability of multiparticulates in clear glass vials.

Test Unit	Time	Strength (HPLC) % Label	Dissolution - Percentage Released (avg) 0.1 N HCl	Secondary dissolution in phosphate buffer
Initial		100.0%	0.9%	91.6%
Ambient Room Temp	1 month	97.2%	0.8%	88.5%
	7 month	108.5%	0.8%	94.1%
30° C./60% RH	1 month	99.3%	0.5%	83.4%
	2 month	98.3%	NA	NA
	3 month	104.4%	0.7%	82.2%
40° C./75% RH	1 month	95.4%	0.7%	86.1[1]
	2 month	97.3%	NA	NA
	3 month	102.7%	0.7%	89.4%

[1]One capsule - 78% released.

EXAMPLE 2

Coated Pantoprazole Sodium Multiparticulate Formulations (Batch B)

Based upon the lab batch A, a further scale-up batch of 1400 g was manufactured using a 7" wurster fluid bed coater. During coating for this batch, the level of hydroxypropyl methyl cellulose initial seal coat was 2% of the weight of the uncoated multiparticulates as compared to 4% for the coated Batch A. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. Also, the talc was added directly to the coating suspension as a larger nozzle size (1 mm) was used.

Initial release of coated multiparticulates in 0.1 N acid was high (9.0%) and very close to the limit of 10%. This Batch (B) did not meet the stability and dissolution criteria when tested at accelerated conditions (30° C./60% relative humidity (RH) and 40° C./75% RH). Trial from this batch indicated that an initial seal coat of greater than 2% of uncoated multiparticulates enhances stability of the multiparticulates. Additionally, more enteric polymer loading may be beneficial to control the release in acid media as the process is scaled up.

EXAMPLE 3

Preparation of Pantoprazole Multiparticulates Scale-Up Batch

A. Technical Batch

Using a NICA extruder/spheronizer, a 36 kg technical batch of uncoated multiparticulates was prepared and 20 kg of this batch were enteric coated in a Glatt GPCG-15 machine to result in a 32 kg batch of coated multiparticulates. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. This batch was filled into size #3 HPMC capsules at a fill weight of 156 mg. The release in 0.1 N HCl at 2 hours was greater than the desired 10%. Based on this, taking into account scale-up effects, minor adjustments were made to the formula and process for clinical batch.

B. Clinical Batch

Two 12 kg sub batches of a wet granulated mass were extruded and spheronized on a NICA extruder/spheronizer resulting in wet multiparticulates. The multiparticulates were tray dried at 40° C. for 10 to 12 hours to the desired % LOD of 3.4% to 4.3%. The batch was screened and only 16 kg of uncoated multiparticulates were used for coating to ensure uniformity and completeness of coating in the GPCG-15 machine. The sieved uncoated multiparticulates were coated with an initial hydroxypropyl methycellulose seal coat, followed by an Eudragit L30D-55 enteric coat, followed by a hydroxypropyl methycellulose final coat to result in 33 kg of coated multiparticulates. This batch was filled into size #2 HPMC capsules at a fill weight of 206 mg.

The release in 0.1 N HCl at 2 hours was less than the 10% limit and in pH 6.8 phosphate buffer, it was greater than the 80% limit at 45 minutes. The batch met in vitro release characteristics. The one month stability date showed that the multiparticulates were stable at 40° C./75% RH for one month. Currently, this batch is stable up to one year at room temperature and upto 6 months at 40 deg.C/75% RH. Stability study at room temperature condition beyond one year is ongoing. The one year room temperature stability results of this batch are shown in the following Table II.

The spheroid filled capsule had a faster in vitro release (dissolution) as compared to the Protonix 40 mg tablet in pH 6.8 phosphate buffer.

TABLE II

Stability of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg

	Test						
	Appearance and Description	Strength (HPLC)	Water (KF)	Purity Specification		Dissolution	
	#2 Opaque white capsules (cap and body) containing white to off-white colored	90.0-110.0% Label Claim (LC)	For Information	Largest Single Known or Unknown Impurity ≤0.5 (RRT)	Total Known and Unknown Impurities ≤2.0	Dissolution in 0.1 N HCl NMT 10% in 2 hrs. Conforms to USP <724>	Dissolution in Phosphate Buffer NLT 75% in 45 min. Conforms to USP <724>
	spheroids	%	%	%	%	%	%
Initial	Conforms	100.3	5.1	BRL	BRL	0	105
Initial (Spheroids only)[a] 25° C./ 60% RH						0	107
1 Month	No Change	99.5	5.2	0.17 (1.39)	0.17	1	103
2 Month	No Change	101.4	4.6	0.15 (1.38)[b]	0.23	0	101
3 Month	No Change	101.2	4.5	0.17 (1.39)	0.17	0	100
6 Month	No Change	101.3	4.5	0.18 (1.38)[b]	0.24	0	100
6 Month (Spheroids only)[a]						0	112
9 Months	No Change	99.2	5.1	0.21 (1.40)[b]	0.33	0	101
9 Months (Spheroids only)[a]						0	108
12 Months	No Change	99.1	5.1	0.08 (0.14)	0.23	0	102
12 Months (Spheroids only)[a]						0	104

BRL = Below Reporting Limit (0.05%). NMT = Not more than. NLT = Not less than. RRT = Relative retention time.

[a]Initial and revalidation dissolution results are provided for Pantoprazole Sodium Spheroids, 40 mg/206 mg, which is the ingoing batch of spheroids used for manufacture of Pantoprazole Sodium Spheroid- filled Capsules, 40 mg.

[b]Corresponds to the impurity at RRT = 1.39.

EXAMPLE 4

Evaluation of Batch a Formulation in Beagle Dogs

The in-vitro release data of the sodium pantoprazole multi particulate formulation shows a faster release than the current marketed tablet. This provides earlier absorption and thereby a faster onset of action. The dog data clearly shows earlier drug levels of sodium pantoprazole from multiparticulates as compared to the single monolithic tablets. Earlier onset of action provides faster relief from gastric pain and other gastrointestinal (GI) disorders.

Pantoprazole sodium formulations have been evaluated in Beagle Dogs (n=5). The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole is illustrated in the Table III below.

As illustrated, the non-optimized lab batch of sodium pantoprazole multiparticulate formulation dosed in dogs shows smaller lag time than the current marketed tablet. In the following table, AUC refers to the area under a curve plotting mean concentration against protocol time. C_{max} refers to the maximum observed concentration value in the blood sample after administration. T_{max} refers to the time point when C max occurs. T_{lag} refers to the time following administration before effective amounts of the drug are observed in the circulation; $t_{1/2}$, (hr) provides the half-life for drug elimination. Relative bioavailability compares the absorption of a product from the gut in comparison with a dose given intravenously (assumed 100%).

TABLE III

The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole

Parameter	20 mg Market Tablet Batch A Pantoprazole Na[a]	40 mg Multiparticulate Capsule Batch A with enteric coat - Pantoprazole Na
AUC (μg*hr/mL)	16.3 (2.46)	17.3 (2.33)
Cmax (μg/mL)	11.7 (3.55)	7.10 (1.76)
Tmax (hr)	1.70 (0.84)	1.20 (0.27)
tlag (hr)	1.10 (0.91)	0.25 (0.18)
t½ (hr)	0.62 (0.17)	0.77 (0.21)
Relative Bioavailability	—	AUC: 106%[b] Cmax: 61%[b]

[a]AUC and Cmax are normalized to a 40 mg dose
[b]Relative to Market Product Tablet

The dog data of the sodium pantoprazole multi particulate formulation gives a similar AUC as the current marketed tablet. Without wishing to be bound by theory, it is believed that the faster release and similar AUC of the multi particulates is achieved by lowering the level of the disintegrating agent crospovidone (as compared to the level in the tablet) and incorporating the functional excipient polysorbate 80 in the core of the spheroids.

EXAMPLE 5

Pantoprazole Sodium Sesquihydrate Excipient Formulations

This study was performed to determine the compatibility of pantoprazole sodium sesquihydrate with hypromellose 2208, sodium lauryl sulfate (SLS), crospovidone, and polysorbate-80.

A. Study Design

The study consists of two sets of samples. The first set contained drug and excipient. The second set contained drug, excipient and approximately 2 μl water. The reason for the water along with the drug and the excipient is to see whether additional water present causes any incompatibility.

The excipients were mixed with the drug in the ratio indicated in the following table. The excipients and the drug were weighed into a glass vial. Then the vials were vortexed for 15 seconds. Similarly, a second set of samples was prepared. Approximately 2 μl (the smallest amount of water that can be added with the pipette in the lab) was added to these vials. Then the vials were vortexed for 5 seconds. Finally, the first and second set of vials were capped and placed in stability chambers. The conditions tested were 40°/75% RH and 51° C. for 3 weeks.

B. Results

The results of this drug-excipient compatibility study are presented as % recovery in the Table IV below. The selection criteria for the compatibility or in-compatibility are based on the % recovery between 90-110%.

TABLE IV

Drug: Excipient Compatibility Results

Excipient	Ratio of Drug: Excipient	% Recovery: Drug + Excipient, 40° C./75% RH 3 weeks	% Recovery: Drug + Excipient, 51° C. 3 weeks	% Recovery: Drug + Excipient + Water, 40° C./75% RH 3 weeks	% Recovery: Drug + Excipient + Water, 51° C. 3 weeks
Control (Drug alone)	—	94.67	100.53	94.60	96.64
Hypromellose 2208, USP, 3 cps	10:1	99.209	93.248	93.811	97.421
Sodium Lauryl Sulfate (SLS)	5:3	99.947	98.763	95.466	95.088
Crospovidone, NF	10:1	100.080	98.908	97.201	105.716
Polysorbate-80, NF BP/EP (vegetable source)	10:1	98.301	90.961	99.908	81.405

From the results shown in the table, the following conclusions can be drawn. Hypromellose 2208, SLS, crospovidone and polysorbate-80 are compatible with pantoprazole sodium sesquihydrate at 40° C./75% RH for 3 weeks. Hypromellose 2208, SLS and crospovidone are compatible with pantoprazole sodium sesquihydrate at 40° C./75% RH and 51° C. with and without additional water for 3 weeks.

In this study degradation compounds were not studied. However, the pediatric clinical formulation, [pantoprazole sodium sesquihydrate 45.24% w/w; microcrystalline cellulose 27.25% w/w; polysorbate 80 5% w/w; crospovidone 15% w/w; hypromellose 2208 1% w/w; sodium carbonate 6.5% w/w; purified water q.s.], was studied under accelerated conditions of 40° C./75% RH and is stable up to 6 months, providing a 2 year room temperature shelf life.

The components of the pediatric formulation are provided in the following Table V.

Formulation:	Multiparticulates	
Ingredients	Amount/Capsule	% w/w
Core:		
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573
Enteric Coat:	100.20 mg	48.67
Eudragit L30D-55	208.00 mg	30.309
	62.40 (solids)	
Talc, USP, Altalc 500V	31.20 mg	15.155
Sodium Hydroxide, NF	9.30 mg	0.175
1 N solution	0.36 (solids)	
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	*removed during processing
Total	204.20 mg	99.186
Final Seal Coat:	1.54 mg	0.748
Hydroxypropyl Methylcellulose, USP 2910, 6 cps	1.54 mg	0.748
Purified water, USP/BP/EP	18.99 mg*	*removed during processing
Total	205.74 mg	99.934
Talc, USP, Altalc 500V	0.14 mg	0.068
Total	205.88 mg	100.002

EXAMPLE 6

Evaluation of Pantoprazole Sodium Formulation in Human Adult Subjects

In this study, 40 mg pantoprazole sodium, formulated as described, clinical pediatric formulation, was administered to healthy human adults (n=24) by sprinkling in applesauce, in tablet form, or as an aqueous suspension prepared using an inactive powder blend and water (8 in each group).

In the following Table VI, column 1 provides the pharmacokinetic (PK) parameters, AUC (area under the concentration curve), AUC_T is the area under the concentration time curve, and C_{max}, maximum concentration. The second column provides the test/reference geometric mean (GM) ratio. The third column provides the confidence interval for the GM ratio. [The FDA considers a test product to be bioequivalent to a reference product if the 90% confidence interval (CI) of the geometric mean ratio of AUC and C_{max} between the test and reference fall within 80-125%]. -The confidence interval is calculated using WinNonlin software.

TABLE VI

Human PK study Results		
PK parameter	Test/Reference GM ratio	90% CI for ratio*
A. Spheroids sprinkled in applesauce:		
AUC	90	84-96
AUC_T	89	84-95
Cmax	62	56-70
B. Spheroids in suspension:		
AUC	94	88-100
AUC_T	94	88-100
Cmax	66	60-74

The lag time in the absorption of the tablet was higher compared to the sprinkle and suspension formulations. The entire drug in the tablet is released over a small time interval and therefore a higher C_{max} is obtained. With the spheroid formulations, drug from each spheroid is released over a longer time interval and therefore the C_{max} is lower than the tablet. However, the period of time following administration that pantoprazole remained in the circulation is similar for the 3 formulations.

All documents identified herein are incorporated by reference. One of skill in the art will recognize that minor modifications to the conditions and techniques described in the specific embodiments described herein can be varied without departing from the present invention. Such minor modification and variants are within the scope of the invention as defined by the following claims.

The invention claimed is:

1. A method of treating ulcers of the stomach and duodenum, gastroesophageal reflux disease (GERD), or Zollinger-Ellison Syndrome in a mammalian subject, comprising the step of administering to the subject a plurality of pantoprazole multiparticulates, each of which comprise:

a core consisting of about 45% w/w pantoprazole sodium sesquihydrate and one or more excipients comprising about 25% to 30% w/w microcrystalline cellulose, about 4% to 6% w/w polysorbate 80, about 14% to 16% w/w crospovidone, about 0.5 to 2% w/w hydroxypropyl methylcellulose, about 5% to 8% w/w sodium carbonate, and about 1 to about 2% water;

an initial seal coat comprising hydroxypropylmethyl cellulose on the spheroid core; and an enteric coat on the initial coated spheroid core,

wherein the multiparticulates have an average size in the range from about 0.7 mm to about 1.25 mm.

2. The method according to claim **1**, wherein the mammalian subject is a human.

3. The method according to claim **1**, wherein said plurality of multiparticulates comprises a pantoprazole compound

present in an amount of about 40 mg of pantoprazole per 100 mg uncoated multiparticulates.

4. The method according to claim **1**, wherein the multiparticulates have an average diameter of about 1 mm.

5. The method according to claim **1**, wherein said enteric coat comprises a copolymer of methacrylic acid and methacrylates

6. The method according to claim **5**, wherein the enteric coat comprises about 48% w/w of the coated multiparticulates.

7. The method according to claim **1**, further comprising a final seal coat on the enteric coat.

8. The method according to claim **7**, wherein the final seal coat comprises about 0.1 to 10 wt% of the multiparticulates.

9. The method according to claim **7**, wherein the final seal coat comprises hydroxypropyl methyl cellulose (hypromellose).

10. The method according to claim **1** wherein said initial seal coat is in the range of about 2 to 4% w/w of the weight of the uncoated core.

11. The method according to claim **1**, wherein the initial seal coat comprises hypromellose.

12. The method according to claim **1**, wherein the spheroid tore consists essentially of:

pantoprazole sodium sesquihydrate	45% w/w
microcrystalline cellulose	27% w/w
polysorbate 80	5% w/w
crospovidone	15% w/w
hydroxypropylmethylcellulose	1% w/w, and
sodium carbonate	7% w/w.

13. The method according to claim **1**, wherein the enteric coating comprises a copolymer of merhaczylic acid and methyacrylates and further comprising an outer seal coat comprising hydroxypropylmethyl cellulose and wherein the multiparticulates have an average diameter of about 1 mm.

14. The method according to claim **1**, wherein the enteric coat comprises about 48% w/w of the multiparticulates.

15. The method according to claim **1**, wherein the enteric coating comprises about 30% w/w of the copolymer of methacrylic acid and methacrylate, about 15% w/w talc, about 3% triethyl citrate and a pH adjuster; said amounts being by weight of the multiparticulates.

16. The method according to claim **1**, wherein the multiparticulates are administered in a food.

17. The method according to claim **16** wherein the food is applesauce.

18. The method according to claim **1**, wherein the multiparticulates are administered in a physiologically compatible liquid.

19. The method according to claim **1**, wherein the multiparticulates are contained in a foil wrapper prior to administration.

20. The method according to claim **1**, wherein the multiparticulates are administered in a capsule.

21. The method according to claim **1**, wherein the spheroid core consists essentially of:

pantoprazole sodium sesquihydrate	about 45% w/w
microcrystalline cellulose	about 27% w/w
polysorbate 80	about 5% w/w
crospovidone	about 15% w/w
hydroxypropylmethylcellulose	about 1% w/w,
sodium carbonate	about 6.5% w/w, and
water.	

* * * * *



(12) **United States Patent**
Venkata Ramana Rao et al.

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(54) **PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS**

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(57) **ABSTRACT**

A method of treating gastroesophageal reflux disease (GERD), ulcers of the stomach or duodenum, or Zollinger-Ellison Syndrome in a human, by administering pantoprazole sodium multiparticulates is described. The pantoprazole multiparticulates have a spheroid core of pantoprazole or an enantiomer thereof, or a salt thereof, a surfactant, and a disintegrant; a sub coat which is comprised of hydroxypropyl methylcellulose (hypromellose) and water, an enteric coat on the subcoat, and a final seal coat over the enteric coat, which is composed of hydroxypropyl methylcellulose (hypromellose) and water.

7 Claims, No Drawings

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PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATION

This is a continuation of U.S. patent application Ser. No. 10/955,567, filed Sep. 30, 2004, which claims the benefit under 35 USC 119(e) of prior U.S. Provisional Patent Application No. 60/507,810, filed Oct. 1, 2003.

BACKGROUND OF THE INVENTION

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole, is a H+/K+-adenosine triphosphate (ATP) inhibitor (also known as acid pump or proton pump inhibitor (PPI), is an enzyme present in the gastric parietal cells. It is believed that these drugs are metabolized in the parietal cells to active sulfenamide metabolites that inactivate the sulfhydryl group of the proton pump, thus reducing the hydrogen ion secretion. PPIs are generally lipophilic weak bases with poor aqueous solubility at low pH. Many PPIs are unstable in low pH solutions and undergo rapid acid-catalyzed degradation, and they are relatively stable at neutral or high pH.

The current commercial oral formulations of sodium pantoprazole are single unit coated tablets. See, e.g., U.S. Pat. No. 5,997,903, which describes oral forms of pantoprazole that consist of a core, an intermediate layer and an outer layer. The current coating has a tendency to cause undesirable sticking of the tablet to the gastrointestinal tract.

Multiparticulate formulations, because of their nature of dispersing in the gastrointestinal tract, show a reduced food effect and variability in gastric emptying times, thereby providing for reduced inter and intra subject variability, as compared to single unit tablets (Intl. Journal of Pharmaceutics 140 [1996] 229-235).

Several unsuccessful attempts have been made in the past to develop a multiparticulate formulation of pantoprazole. However, these attempts yielded multiparticulates that were not bioequivalent to tablets, only 70% relative bioavailability was found. Another attempt using different technologies-non-pareil seed coating and extrusion/spheronization, resulted in a product that did not provide the appropriate release in acid conditions. In addition, these attempts yielded product that was unstable, as observed by discoloration, when stored at room temperature.

SUMMARY OF THE INVENTION

The invention provides a stable multiparticulate pantoprazole formulation that provides reduced inter and intra subject variability.

In one embodiment, the pantoprazole multiparticulates of the invention is composed of a spheroid core comprising pantoprazole or an enantiomer thereof, or a salt or hydrate thereof, at least one surfactant, at least one disintegrant, and about 1% to about 2% w/w water; an enteric coat on the core, said enteric coat comprising a copolymer of methacrylic acid and methacrylates in the range of about 15 to about 45 % w/w of the spheroid core; wherein said multiparticulates have an average size of about 1 mm in diameter.

Advantageously, the multiparticulate formulations of the invention are stable under room temperature storage conditions for at least twelve months. Based on the trend analysis using the twelve month room temperature data and 6 month 40° C./75% relative humidity (RH) data available to date, the multiparticulates of the invention should have a shelf life of over 2 years. Typically, a multiparticulate formulation of the invention is considered stable if it retains 90% to 110% of its potency during shelf life storage.

This pantoprazole multiparticulate formulation of the invention is less prone to adherence to the intestinal walls, nasogastric and gastromy tubes, and pouch material thereby giving predictable delivery of the drug product to the site of drug release. It also provides for an early onset of action for relief of gastrointestinal pain and has a prolonged duration of action. This formulation allows dosing to pediatric patients and patients who have difficulty swallowing solid foods. This formulation also allows for drug delivery via nasogastric and gastrostomy tubes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a multiparticulate formulation of pantoprazole having a unique combination of excipients and a surfactant (e.g., polysorbate 80) that are compatible with pantoprazole sodium in the presence of an alkaline pH environment. Further, the invention provides a process that utilizes low shear during granulation and low temperature during drying for preparation of the multiparticulate. This process contributes to the stability of the core of the multiparticulates of the invention.

In one aspect, the invention provides multiparticulate formulations of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, i.e., in the lower gastrointestinal tract.

The multi particulate formulation of sodium pantoprazole of the invention provides an enhanced system for the delivery of pantoprazole to patients. The current marketed formulation is a single monolithic tablet. The present formulation of multiparticulate spheroids, which is adaptable for use in a capsule or a foil packet, can be prepared by extrusion/spheronization plus coating technology.

The composition of the multiparticulate of the invention, and the enteric coat, e.g., Eudragit, allows for reduced release at low pH (~1) and fast release at a neutral pH (~7). This provides faster blood levels of the drug, in patients, and thereby a faster onset of action. The smaller T_{lag} value of multiparticulate formulation as compared to that of a single monolithic tablet based on the results from dog data indicates faster onset of action of multiparticulate formulation.

The use of a multi particulate formulation facilitates dosing to pediatric patients and patients who have trouble swallowing, by dispersing the spheroids in a suspending liquid or sprinkling/dispersing in a low pH liquid like applesauce, prior to administration. The suspending liquid could be made prior to administration by mixing a blend of powder material with water. The smaller size of the multi particulates, in a capsule or pouch or any other container, also allows dosing through nasogastric or gastrostomy tube.

This formulation allows for a faster relief of GI pain, and prolonged duration of action (extended release), as compared to the current marketed tablet.

I. Multiparticulates of the Invention

Suitably, the multiparticulates are in the range of about 0.1 to 2 mm, or 0.5 mm to 1.5 mm, or 0.7 mm to 1.25 mm, or 0.8 mm to 1 mm. In one embodiment, the multiparticulates in a composition of the invention average about 1 mm in diameter. Typically, the multiparticulates of the invention are no greater than about 1 mm in size in order to facilitate passage through nasogastric tubes

The multiparticulates of the invention are composed, at a minimum, of a spheroid core with an enteric coat over the core. In between the core and enteric coat an initial seal coat may be applied, e.g., comprising a coating of hydroxylpropyl methylcellulose (hypromellose). Also, over the enteric coat a final seal coat may be applied, e.g., a coating of hydroxylpropyl methyl cellulose (hypromellose). The spheroid core is composed of, at a minimum, a pantoprazole or a salt thereof, and a surfactant.

As used herein unless the context requires otherwise, the term 'pantoprazole' refers to 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole and enantiomers thereof and the term 'pantoprazole compound' includes pantoprazole and enantiomers and salts and hydrates thereof. The active compound, pantoprazole is described in European Patent 166 287, which describes the preparation thereof, and is available commercially under the brand name PROTONIX®. Examples of pharmaceutically acceptable salts of pantoprazole include, e.g., sodium, magnesium, and calcium, among others; still others are described in the European Patent 166 286, which is incorporated by reference herein. The selection of a suitable salt is not a limitation of the invention. In one embodiment, the salt is sodium. Typically, the pantoprazole compound is present in the range of from about 5 to 50% w/w, more preferably about 20 to 45% w/w, of the total multiparticulate.

Suitable surfactants are known to those of skill in the art. However, particularly desirable are sodium lauryl sulfate, polysorbates, including, e.g., polysorbate 80, and mixtures of these components. Typically, the surfactant is present in the core in an amount of about 2 to about 7% w/w, and desirably, about 5% w/w of the core. In another embodiment, the surfactant is present in a ratio of about 5:3 drug: surfactant (e.g., pantoprazole sodium sesquihydrate to sodium lauryl sulfate) to about 10:1 drug: surfactant (e.g., pantoprazole sodium sesquihydrate to polysorbate 80). Advantageously, the surfactants in the multiparticulate formulation have been found to enhance the wettability and, thus, the speed and extent of release and absorption of the sodium pantoprazole, from the multi particulate formulation of the invention.

The spheroid core can further contain a disintegrant, a pH adjuster and, optionally a binder or another excipient such as hydroxypropyl methylcellulose (e.g., hypromellose 2208). Suitably, the total amount of disintegrant(s) present in the core is an amount of about 15% w/w to about 80% w/w, or about 20% w/w to about 70% w/w, or about 25% w/w to about 45% w/w, or about 30% w/w to about 42% w/w. In one embodiment, the total amount of drug to binder is represented by a ratio of from about 50:1 to about 40:1 by weight drug: binder. The total amount of a pH adjuster in the formulation can range from about 0.1% w/w to about 10% w/w of the multiparticulate, or about 1% w/w to about 8% w/w, or about 3% w/w to about 7% w/w. However, these percentages can be adjusted as needed or desired by one of skill in the art.

The disintegrant may be selected from among other known disintegrants, including, e.g., cellulose, and crospovidone, among others. In one embodiment, the disintegrant is selected from among microcrystalline cellulose and crospovidone, and mixtures thereof. The binder may be selected from among known binders, including e.g., cellulose, and povidone, among others. In one embodiment, the binder is hydroxylpropyl methyl cellulose (hypromellose). Suitable pH adjusters include, e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate, among others. Still other suitable components will be readily apparent to one of skill in the art.

In one embodiment, the spheroid core contains, w/w based on the dry uncoated core, about 45% pantoprazole sodium sesquihydrate (about 40% free pantoprazole) , about 25 to 30%, and preferably about 27% microcrystalline cellulose, about 4 to 6%, and preferably about 5% polysorbate 80, about 14 to 16%, and preferably about 15% crospovidone, about 0.5 to 2%, and preferably about 1% hypromellose 2208, about 5 to 8%, and preferably about 6.5% sodium carbonate. In one embodiment, the spheroid core contains:

pantoprazole sodium sesquihydrate	45.24% w/w
microcrystalline cellulose	27.25% w/w
polysorbate 80	5% w/w
crospovidone	15% w/w
hypromellose 2208	1% w/w
sodium carbonate	6.5% w/w

In another embodiment, the spheroid core contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573

Although moisture is removed from the core during the drying process which is described below, the core preferably retains about 1% to about 2% w/w water. Without wishing to be bound by theory, the inventors believe that this water content contributes the stability of this multiparticulate as compared to the failed prior art attempts at forming a multiparticulate pantoprazole.

Optionally, an initial seal coat (or subcoat) can be applied directly to the core prior to coating with the enteric coat. Although the components of this seal coat can be modified by one of skill in the art, a particularly suitable initial seal coat is composed of hydroxypropyl methylcellulose (hypromellose) and water. For example, a suitable initial seal coat can be applied as a 7.5% w/w hypromellose solution. Typically, such a seal coat is in the range of about 2% w/w to about 4% w/w of the uncoated core or about 1% w/w to about 2% w/w of the coated multiparticulate.

In one embodiment, a multiparticulate with a subcoat contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
A. Sub Coat:	4.00 mg	1.943
Pantoprazole Sodium Pellets (40 mg pantoprazole per 100 mg pellets)	100.00 mg	48.573
Hydroxypropylmethyl cellulose 2910, USP, 6 cps	4.00 mg	1.943
Purified water, USP/BP/EP *removed during processing	9.33 mg*	
Total	104.00 mg	50.516

The enteric coat is applied over the initial seal coat, if present, or directly to the uncoated spheroid core. Suitably, the enteric coat is applied such that it coats the core in an amount of about 15 to 45% w/w, or about 20% w/w to about 30% w/w, or about 25% w/w to 30% w/w of the multiparticulate. In one embodiment, the enteric coat is about 27.5 to 32.5% w/w of the multiparticulate. Suitably, the enteric coat contains a product which is a copolymer of methacrylic acid and methacrylates, such as the commercially available Eudragit L 30D-55. In one embodiment, the enteric coat is composed of a Eudragit L30D-55 copolymer, talc, triethyl citrate, sodium hydroxide and water. More particularly, the enteric coating may contain about 30% w/w of multiparticulate (applied as a 30 wt % dispersion) of Eudragit L 30D-55 coating; about 15% w/w talc, about 3% triethyl citrate; a pH adjuster such as sodium hydroxide and water. Other suitable materials may be selected for use in the enteric coat including, e.g., hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and the like.

In one embodiment, a multiparticulate of the invention is provided with a subcoat over the core and an enteric coat as follows:

Ingredients	Amount/capsule	% w/w, based on total weight multiparticulate
Core + Subcoat	100.20 mg	48.67
Eudragit L30D-55	208.00 mg 62.40 (solids)	30.309
Talc, USP, Altalc 500 V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N	9.30 mg	0.175

-continued

Ingredients	Amount/capsule	% w/w, based on total weight multiparticulate
solution	0.36 (solids)	
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	
*removed during processing		
Total	204.20 mg	99.186

In one embodiment, the enteric-coated multiparticulate is further coated with a final seal coat. Suitably, this final seal coat is comprises hydroxypropyl methylcellulose, and about 0.1% w/w to 10% w/w of the coated multiparticulate, 0.1% w/w to about 5% w/w, or about 0.2% w/w to about 4% w/w.

In one embodiment, a final seal coat of hydroxypropyl methylcellulose in an amount of 0.5 to 1% w/w of the multiparticulate in water (which is removed during processing) is applied over the enteric coat. Following this, a coating of talc can optionally be applied over the final seal coat, in an amount of about 0.05 w/w to about 1% w/w, and preferably 0.1% w/w to 0.5% w/w.

In one embodiment, the resulting multiparticulate formulation of the invention achieves a geometric mean AUC ratio of test/reference of 89 to 94 with a 90% confidence interval of 84 to 100 for the ratio or achieving a geometric mean Cmax ratio of test/reference of 62 to 66 with a 90% confidence interval of 56 to 74 for the ratio or an in-vitro dissolution profile as shown below:

		% Drug Release			
Media	Time	Initial	6 Months @ 25 C./60% RH	6 Months @ 40 C./75% RH	Target
Acid (pH 1.0)	2 hrs	0.33	0.45	0.6	NMT 10%
Followed by	3 min	—	0.91	0.85	—
Alkaline	6 min	—	3.61	1.83	—
Buffer	9 min	—	52.25	16.45	—
(pH 6.8)	12 min	—	89.65	75.15	—
	15 min	101.58	97.15	91.92	—
	30 min	105.29	100.67	98.96	—
	45 min	105.29	100.57	99.14	NLT 75%
	60 min	105.06	100.52	99.07	—

In another embodiment, the resulting multiparticulate formulation of the invention achieves a mean AUC of 5451 to 5629 ng.h/ml and mean Cmax of 1865 to 1929 ng/ml or an in-vitro dissolution profile as shown below:

	% Drug Release*			
	Acid	Buffer (min)		
Batch	2 hrs	15	30	45
Initial	0.08	101.77	107.44	107.38
6 Months @ 40 C./75% RH	0.73	95.44	101.12	101.21
12 Months @ 25 C./60% RH	0.30	96.11	101.92	102.20

*Specifications: Acid at 2 hrs - NMT 10.0%; Buffer at 45 min - NLT 75%

However, the invention is not limited to these exemplary profiles.

Without wishing to be bound by theory, it is believed that final seal coat layer of hydroxypropyl methylcellulose provides a physical barrier for reduced contact between the mucoadhesive Eudragit layer and the upper GI tract, and thereby allows the reliable transit of the multiparticulates to the proper pH environment in the GI tract for effective release and absorption of the drug. In addition, the final seal coat layer of hydroxypropyl methylcellulose imparts anti-sticking properties to the multiparticulates and thus the multiparticulates are not sticking to the pouch material and/or nasogastric tube. The multiparticulates of the invention are useful for administration via the nasogastric tube and via food vehicles, particularly acidic food vehicles.

II. Method of Producing Multiparticulate Formulations of Invention

In another aspect, the invention provides a method of producing the multiparticulate formulations of the invention.

Typically, the uncoated pantoprazole compounds are prepared are follows. The dry components, including, at least the pantoprazole compound and the binder are dry blended in a suitable mixer under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for the selected equipment. Optionally, hydroxypropyl methylcellulose or crospovidone may be substituted or additionally included in this step. Additionally, a pH adjuster may be included in this step.

Subsequently, the liquid components, e.g., the surfactant and water, are mixed in to afford a granulated product by mixing under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for the selected equipment. The granulation is then extruded and spheronized through a suitable device (e.g., a NICA extruder/spheronizer) and the resulting spheroids are dried, sifted, and optionally blended prior to storage.

The inventors have found that a significant advantage is provided to the stability of the compound when the multiparticulates of the invention are dried at low temperature. Desirably, the spheroid cores of the pantoprazole multiparticulates of the invention are dried to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%. As used herein, low temperature drying refers to a temperature not exceeding about 40° C. for a period of 10 to 12 hours. When the drying conditions exceed this temperature and time period, impurities are observed that contribute to instability. In one embodiment, drying of the core is performed in the range of 35° C. to 40° C., or about 37° C. to 39° C. for about 8 to 72 hours. In another embodiment, the core is dryed at about 40° C. for 10 to 12 hours. Suitably, when coating layers are applied as described, the drying temperature for the various coating layers is also in this range.

Optionally, an initial seal coat of a hydrophilic polymer can be applied to the uncoated multiparticulates. For example, an initial seal coat composed of hydroxypropyl methylcellulose and purified water can be applied on a fluid bed coater, e.g., by spraying.

The enteric coat can be applied directly to the uncoated spheroid core, i.e., the uncoated multiparticulate, or may be applied over an initial seal coat. The enteric coat as described above, is typically applied on a fluid bed wurster coater.

In one embodiment, a final seal coat is applied over the enteric coat and, optionally, talc is utilized in the final step prior to filling the multiparticulates into a suitable packaging unit.

The multiparticulate of the invention may be in any suitable form including, e.g., granules, pellets, beads, minitabs, spherules, beadlets, microcapsules, millispheres, nanocapsules, microspheres, platelets, tablets, and capsules, depending upon the desired route of delivery.

III. Formulations, Kits and Methods of Delivery

In another embodiment, the present invention provides products containing the pantoprazole multiparticulates of the invention.

Suitably, the multiparticulate compositions of the invention are formulated such that a patient receives a suitable amount of the pantoprazole, e.g., 5 mg to 200 mg, about 10 mg to about 100 mg, or about 40 mg (measured based upon free pantoprazole). Preferably, the formulations are such that a suitable dose is delivered in a single dosage unit. These doses may be administered daily for a suitable period of time, e.g., 4 weeks to 8 weeks, but can be delivered for a shorter period of time, e.g., 3 days to 3 weeks, one week to 3 months, or over a longer period, e.g., over 6 months, or longer. These compositions can be delivered alone or in combination with an antacid or other suitable composition.

In one embodiment, the invention provides a method of treating humans by administering an effective dose of the pantoprazole multiparticulates such that an area under curve (AUC) at least bioequivalent to Protonix® 40mg tablet and Cmax as listed in Table VI are achieved.

In one embodiment, the pantoprazole multiparticulates are packaged for use by the patient or his caregiver. For example, the multiparticulates can be packaged in a foil or other suitable package and is suitable for mixing into a food product (e.g., applesauce and other acidic food vehicles) or into a drink for consumption by the patient.

The pantoprazole multiparticulate formulations of the invention are useful for treatment of gastroesophageal reflux disease (GERD), ulcers of the stomach and duodenum, and Zollinger-Ellison Syndrome.

In another embodiment, the pantoprazole multiparticulates are suspended in a physiologically compatible suspending liquid.

In yet another embodiment, the pantoprazole multiparticulates are filled in capsules, caplets or the like for oral delivery.

In still a further embodiment, the invention provides method of treating a subject in need thereof by administering an effective dose of the pantoprazole multiparticles of the invention.

The following examples illustrate specific embodiments of the invention and are not a limitation on the present invention.

EXAMPLE 1

Pantoprazole Sodium Multiparticulate Formulations

Using a NICA extruder/spheronizer, during initial formulation development, several prototypes of uncoated multiparticulates were manufactured to obtain a target immediate release profile similar to or faster than the pantoprazole sodium uncoated tablet, currently available as Protonix (20 mg and 40 mg) tablets. Levels of the disintegrant crospovidone from 5 to 28.5% and the binder hydroxypropyl methyl cellulose from 0.5 to 1% were evaluated during preparation of uncoated multiparticulates over four batches.

A. Preparation of Uncoated Pantoprazole Sodium Multiparticulates

More particularly, pantoprazole sodium sesquihydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (hypromellose 2208), crospovidone and sodium carbonate are dry blended in a Hobart mixer. Thereafter, polysorbate 80, NF (vegetable source) and purified water, USP, are added to the Hobart mixer. The resulting granulated produce is extruded and spheronized in a NICA® extruder/spheronizer and the spheroids are tray dried at a temperature not beyond 40° C. and sifted, followed by transfer to a PK blender. The final spheroids are stored in drums.

One of the batches (an approximately 200 gm batch) with 15% disintegrant crospovidone and with 1% hydroxypropyl methylcellulose (Hypromellose 2208)-was selected as a prototype with similar release profile. The sieve cut of the uncoated spheroids from this batch was between 500-1000 microns.

B. Prototype Lab Batch (Batch A)

Approximately 100 grams of these uncoated spheroids were coated in a 3" Wurster Fluid Bed coater with Eudragit L30D-55 and hypromellose to result in Enteric coated multiparticulates.

During coating for this batch, the level of hydroxypropyl methyl cellulose (HPMC) initial seal coat was 4% of the weight of the uncoated multiparticulates. The % w/w of the dry polymer Eudragit L30D-55 used was 22.16%. In the coating batch, talc was introduced as dry powder in the coating chamber instead of being a part of the suspension. This was due to the small nozzle size (0.5 mm) used for coating the 100 g batch, which could potentially be clogged. The percent of talc and triethyl citrate used for the lab batch was less as compared to the clinical batches which were subsequently prepared. The multiparticulates were hand filled into size #2 HPMC capsules at a fill weight of 206 mg. The capsules were tested in vitro in 0.1 N HCl and pH 6.8 phosphate buffer. Less than 1% was released in acid media in 2 hours and greater than 80% was released in basic media in 45 minutes as desired.

These capsules were tested in dogs. The C_{max} and AUC were compared against the current marketed Protonix 20 mg tablet (and values were extrapolated to the 40 mg strength). It was seen that these multiparticulates released drug at a much faster rate than the current Protonix tablet in pH 6.8 phosphate buffer as desired. The final seal coat comprises hydroxypropyl methylcellulose (hypromellose) and water. This batch was packaged as spheroids in clear glass vials and placed on stability at accelerated conditions (30° C./65% relative humidity (RH) and 40° C./75% RH). The stability was monitored for 3 months. The potency and dissolution results are presented in Table I. The multiparticulates were stable over the three month period and a 40 mg equivalent dose of multiparticulates filled into capsules at each stability time point met all dissolution and stability criteria

Dissolution was tested by filling the stored spheroids into capsule shells, and dissolving in 0.1 N HCl (target release at 2 hours: not more than (NMT) 10%), followed by dissolution in pH 6.8 phosphate buffer (target release at 45 min: not less than (NLT) 75%. The acceptance criteria further required a strength of 90 to 110% of the label claim.

TABLE I

Stability of multiparticulates in clear glass vials.

Test Unit	Time	Strength (HPLC) % Label	Dissolution - Percentage Released (avg) 0.1 N HCl	Secondary dissolution in phosphate buffer
Initial		100.0%	0.9%	91.6%
Ambient Room Temp	1 month	97.2%	0.8%	88.5%
	7 month	108.5%	0.8%	94.1%
30° C./60% RH	1 month	99.3%	0.5%	83.4%
	2 month	98.3%	NA	NA
	3 month	104.4%	0.7%	82.2%
40° C./75% RH	1 month	95.4%	0.7%	86.1[1]
	2 month	97.3%	NA	NA
	3 month	102.7%	0.7%	89.4%

[1]One capsule - 78% released.

EXAMPLE 2

Coated Pantoprazole Sodium Multiparticulate Formulations (Batch B)

Based upon the lab batch A, a further scale-up batch of 1400 g was manufactured using a 7" wurster fluid bed coater. During coating for this batch, the level of hydroxypropyl methyl cellulose initial seal coat was 2% of the weight of the uncoated multiparticulates as compared to 4% for the coated Batch A. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. Also, the talc was added directly to the coating suspension as a larger nozzle size (1 mm) was used.

Initial release of coated multiparticulates in 0.1 N acid was high (9.0%) and very close to the limit of 10%. This Batch (B) did not meet the stability and dissolution criteria when tested at accelerated conditions (30° C./60% relative humidity (RH) and 40° C./75% RH). Trial from this batch indicated that an initial seal coat of greater than 2% of uncoated multiparticulates enhances stability of the multiparticulates. Additionally, more enteric polymer loading may be beneficial to control the release in acid media as the process is scaled up.

EXAMPLE 3

Preparation of Pantoprazole Multiparticulates Scale-Up Batch

A. Technical Batch

Using a NICA extruder/spheronizer, a 36 kg technical batch of uncoated multiparticulates was prepared and 20 kg of this batch were enteric coated in a Glatt GPCG-15 machine to result in a 32 kg batch of coated multiparticulates. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. This batch was filled into size #3 HPMC capsules at a fill weight of 156 mg. The release in 0.1 N HCl at 2 hours was greater than the desired 10%. Based on this, taking into account scale-up effects, minor adjustments were made to the formula and process for clinical batch.

B. Clinical Batch

Two 12 kg sub batches of a wet granulated mass were extruded and spheronized on a NICA extruder/spheronizer resulting in wet multiparticulates. The multiparticulates were tray dried at 40° C. for 10 to 12 hours to the desired % LOD of 3.4% to 4.3%. The batch was screened and only 16 kg of uncoated multiparticulates were used for coating to ensure

uniformity and completeness of coating in the GPCG-15 machine. The sieved uncoated multiparticulates were coated with an initial hydroxypropyl methycellulose seal coat, followed by an Eudragit L30D-55 enteric coat, followed by a hydroxypropyl methycellulose final coat to result in 33 kg of coated multiparticulates. This batch was filled into size #2 HPMC capsules at a fill weight of 206 mg.

The release in 0.1 N HCl at 2 hours was less than the 10% limit and in pH 6.8 phosphate buffer, it was greater than the 80% limit at 45 minutes. The batch met in vitro release characteristics. The one month stability date showed that the multiparticulates were stable at 40° C./75% RH for one month. Currently, this batch is stable up to one year at room temperature and upto 6 months at 40 deg.C/75% RH. Stability study at room temperature condition beyond one year is ongoing. The one year room temperature stability results of this batch are shown in the following Table II.

The spheroid filled capsule had a faster in vitro release (dissolution) as compared to the Protonix 40 mg tablet in pH 6.8 phosphate buffer.

TABLE II

Stability of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg

		Test					
	Appearance and Description	Strength (HPLC)	Water (KF)	Purity Specification		Dissolution	
	#2 Opaque white capsules (cap and body) containing white to off-white colored spheroids	90.0-110.0% Label Claim (LC)	For Information	Largest Single Known or Unknown Impurity ≤0.5 (RRT)	Total Known and Unknown Impurities ≤2.0	Dissolution in 0.1 N HCl NMT 10% in 2 hrs. Conforms to USP <724>	Dissolution in Phosphate Buffer NLT 75% in 45 min. Conforms to USP <724>
		%	%	%	%	%	%
Initial	Conforms	100.3	5.1	BRL	BRL	0	105
Initial (Spheroids only)[a]						0	107
25° C./ 60% RH							
1 Month	No Change	99.5	5.2	0.17 (1.39)	0.17	1	103
2 Month	No Change	101.4	4.6	0.15 (1.38)[b]	0.23	0	101
3 Month	No Change	101.2	4.5	0.17 (1.39)	0.17	0	100
6 Month	No Change	101.3	4.5	0.18 (1.38)[b]	0.24	0	100
6 Month (Spheroids only)[a]						0	112
9 Months	No Change	99.2	5.1	0.21 (1.40)[b]	0.33	0	101
9 Months (Spheroids only)[a]						0	108
12 Months	No Change	99.1	5.1	0.08 (0.14)	0.23	0	102
12 Months (Spheroids only)[a]						0	104

BRL = Below Reporting Limit (0.05%).
NMT = Not more than.
NLT = Not less than.
RRT = Relative retention time.
[a]Initial and revalidation dissolution results are provided for Pantoprazole Sodium Spheroids, 40 mg/206 mg, which is the ingoing batch of spheroids used for manufacture of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg.
[b]Corresponds to the impurity at RRT = 1.39.

EXAMPLE 4

Evaluation of Batch A Formulation in Beagle Dogs

The in-vitro release data of the sodium pantoprazole multi particulate formulation shows a faster release than the current marketed tablet. This provides earlier absorption and thereby a faster onset of action. The dog data clearly shows earlier drug levels of sodium pantoprazole from multiparticulates as compared to the single monolithic tablets. Earlier onset of action provides faster relief from gastric pain and other gastrointestinal (GI) disorders.

Pantoprazole sodium formulations have been evaluated in Beagle Dogs (n=5). The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole is illustrated in the Table III below.

As illustrated, the non-optimized lab batch of sodium pantoprazole multiparticulate formulation dosed in dogs shows smaller lag time than the current marketed tablet. In the following table, AUC refers to the area under a curve plotting mean concentration against protocol time. C_{max} refers to the maximum observed concentration value in the blood sample after administration. T_{max} refers to the time point when C max occurs. T_{lag} refers to the time following administration before effective amounts of the drug are observed in the circulation; $t_{1/2}$ (hr) provides the half-life for drug elimination. Relative bioavailability compares the absorption of a product from the gut in comparison with a dose given intravenously (assumed 100%).

TABLE III

The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole

Parameter	20 mg Market Tablet Batch A Pantoprazole Na[a]	40 mg Multiparticulate Capsule Batch A with enteric coat - Pantoprazole Na
AUC (μg * hr/mL)	16.3 (2.46)	17.3 (2.33)
Cmax (μg/mL)	11.7 (3.55)	7.10 (1.76)
Tmax (hr)	1.70 (0.84)	1.20 (0.27)
tlag (hr)	1.10 (0.91)	0.25 (0.18)
t½ (hr)	0.62 (0.17)	0.77 (0.21)
Relative Bioavailability	—	AUC: 106%[b] Cmax: 61%[b]

[a]AUC and Cmax are normalized to a 40 mg dose
[b]Relative to Market Product Tablet

The dog data of the sodium pantoprazole multi particulate formulation gives a similar AUC as the current marketed tablet. Without wishing to be bound by theory, it is believed that the faster release and similar AUC of the multi particulates is achieved by lowering the level of the disintegrating agent crospovidone (as compared to the level in the tablet) and incorporating the functional excipient polysorbate 80 in the core of the spheroids.

EXAMPLE 5

Pantoprazole Sodium Sesquihydrate :Excipient Formulations

This study was performed to determine the compatibility of pantoprazole sodium sesquihydrate with hypromellose 2208, sodium lauryl sulfate (SLS), crospovidone, and polysorbate-80.

A. Study Design

The study consists of two sets of samples. The first set contained drug and excipient. The second set contained drug, excipient and approximately 2 μl water. The reason for the water along with the drug and the excipient is to see whether additional water present causes any incompatibility.

The excipients were mixed with the drug in the ratio indicated in the following table. The excipients and the drug were weighed into a glass vial. Then the vials were vortexed for 15 seconds. Similarly, a second set of samples was prepared. Approximately 2 μl (the smallest amount of water that can be added with the pipette in the lab) was added to these vials. Then the vials were vortexed for 5 seconds. Finally, the first and second set of vials were capped and placed in stability chambers. The conditions tested were 40°/75% RH and 51° C. for 3 weeks.

B. Results

The results of this drug-excipient compatibility study are presented as % recovery in the Table IV below. The selection criteria for the compatibility or incompatibility are based on the % recovery between 90-110%.

TABLE IV

Drug:Excipient Compatibility Results

Excipient	Ratio of Drug:Excipient	% Recovery: Drug + Excipient, 40° C./75% RH 3 weeks	% Recovery: Drug + Excipient, 51° C. 3 weeks	% Recovery: Drug + Excipient + Water, 40° C./75% RH 3 weeks	% Recovery: Drug + Excipient + Water, 51° C. 3 weeks
Control (Drug alone)	—	94.67	100.53	94.60	96.64
Hypromellose 2208, USP, 3 cps	10:1	99.209	93.248	93.811	97.421
Sodium Lauryl Sulfate (SLS)	5:3	99.947	98.763	95.466	95.088
Crospovidone, NF	10:1	100.080	98.908	97.201	105.716
Polysorbate-80, NF BP/EP (vegetable source)	10:1	98.301	90.961	99.908	81.405

From the results shown in the table, the following conclusions can be drawn. Hypromellose 2208, SLS, crospovidone and polysorbate-80 are compatible with pantoprazole sodium sesquihydrate at 40° C./75% RH for 3 weeks. Hypromellose 2208, SLS and crospovidone are compatible with pantoprazole sodium sesquihydrate at 40° C./75%RH and 51° C. with and without additional water for 3 weeks.

In this study degradation compounds were not studied. However, the pediatric clinical formulation, [pantoprazole sodium sesquihydrate 45.24% w/w; microcrystalline cellulose 27.25% w/w; polysorbate 80 5% w/w; crospovidone

15% w/w; hypromellose 2208 1% w/w; sodium carbonate 6.5% w/w; purified water q.s.], was studied under accelerated conditions of 40° C./75% RH and is stable up to 6 months, providing a 2 year room temperature shelf life.

The components of the pediatric formulation are provided in the following Table V.

Formulation:	Multiparticulates	
Ingredients	Amount/Capsule	% w/w
Core:		
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573
Enteric Coat:	100.20 mg	48.67
Eudragit L30D-55	208.00 mg	30.309
	62.40 (solids)	
Talc, USP, Altalc 500 V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N	9.30 mg	0.175
solution	0.36 (solids)	
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	*removed during processing
Total	204.20 mg	99.186
Final Seal Coat:	1.54 mg	0.748
Hydroxypropyl Methylcellulose, USP 2910, 6 cps	1.54 mg	0.748
Purified water, USP/BP/EP	18.99 mg*	*removed during processing
Total	205.74 mg	99.934
Talc, USP, Altalc 500 V	0.14 mg	0.068
Total	205.88 mg	100.002

EXAMPLE 6

Evaluation of Pantoprazole Sodium Formulation in Human Adult Subjects

In this study, 40 mg pantoprazole sodium, formulated as described, clinical pediatric formulation, was administered to healthy human adults (n=24) by sprinkling in applesauce, in tablet form, or as an aqueous suspension prepared using an inactive powder blend and water (8 in each group).

In the following Table VI, column 1 provides the pharmacokinetic (PK) parameters, AUC (area under the concentration curve), AUC_T is the area under the concentration time curve, and C_{max}, maximum concentration. The second column provides the test/reference geometric mean (GM) ratio. The third column provides the confidence interval for the GM ratio. [The FDA considers a test product to be bioequivalent to a reference product if the 90% confidence interval (CI) of the geometric mean ratio of AUC and C_{max} between the test and reference fall within 80-125%].—The confidence interval is calculated using WinNonlin software.

TABLE VI

Human PK study Results		
PK parameter	Test/Reference GM ratio	90% CI for ratio*
A. Spheroids sprinkled in applesauce:		
AUC	90	84-96
AUC_T	89	84-95
Cmax	62	56-70
B. Spheroids in suspension:		
AUC	94	88-100
AUC_T	94	88-100
Cmax	66	60-74

The lag time in the absorption of the tablet was higher compared to the sprinkle and suspension formulations. The entire drug in the tablet is released over a small time interval and therefore a higher C_{max} is obtained. With the spheroid formulations, drug from each spheroid is released over a longer time interval and therefore the C_{max} is lower than the tablet. However, the period of time following administration that pantoprazole remained in the circulation is similar for the 3 formulations.

All documents identified herein are incorporated by reference. One of skill in the art will recognize that minor modifications to the conditions and techniques described in the specific embodiments described herein can be varied without departing from the present invention. Such minor modification and variants are within the scope of the invention as defined by the following claims.

The invention claimed is:

1. A method of treating gastroesophageal reflux disease (GERD), ulcers of the stomach or duodenum, or Zollinger-Ellison Syndrome in a human,

comprising administering a plurality of pantoprazole sodium multiparticulates to a human, wherein said multiparticulates comprise a core consisting of about 45% w/w pantoprazole sodium sesquihydrate and one or more excipients comprising about 25% to 30% w/w microcrystalline cellulose, about 4% to 6% w/w polysorbate 80, about 14% to 16% w/w crospovidone, about 0.5 to 2% w/w hydroxypropyl methylcellulose, about 5% to 8% w/w sodium carbonate, and about 1 to about 2% water, an inner seal coat surrounding said core, and an enteric coating on the inner seal-coated core, said multiparticulates having an average diameter of about 0.7 mm to about 1.25 mm, and

wherein following administration to humans said composition provides a geometric mean AUC of between 5451 to 5629 ng.h/mL and a geometric mean Cmax of between 1865 to 1929 ng/mL.

2. The method according to claim 1, wherein the multiparticulates have spheroid cores comprising a pantoprazole compound present in an amount of about 40 mg of pantoprazole per 100 mg uncoated multiparticulates, wherein the amount of pantoprazole is measured in the free drug form.

3. The method according to claim 1, wherein the multiparticulates further comprise a final seal coat on the enteric coat.

4. The method of claim 1 wherein the multiparticulates are administered in a physiologically compatible liquid.

5. The method of claim 1 wherein the multiparticulates are administered in a food.

6. The method of claim 1 wherein the multiparticulates are administered in a capsule.

7. The method of claim 1 wherein the multiparticulates are contained within a foil package prior to administration.

* * * * *

US007585283B2

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

(10) **Patent No.: US 7,585,283 B2**
(45) **Date of Patent: Sep. 8, 2009**

(54) **DEVICE AND METHOD FOR EXAMINING A BODY LUMEN**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 628 days.

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See application file for complete search history.

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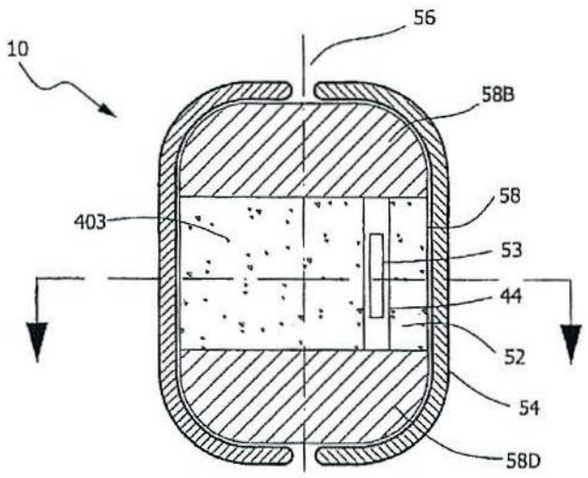
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(57) **ABSTRACT**

A device and method is described for enabling an examining device to pass through an abnormally configured body lumen. The device may pass through a body lumen while maintaining an initial dimension. Upon encounter with an abnormally configured body lumen, the device may be depleted and take on a final dimension after a predetermined time period, regardless of its current orientation with respect to the body lumen, so that the device may pass through and vacate the abnormally configured body lumen shortly after the predetermined time period may have elapsed.

27 Claims, 2 Drawing Sheets



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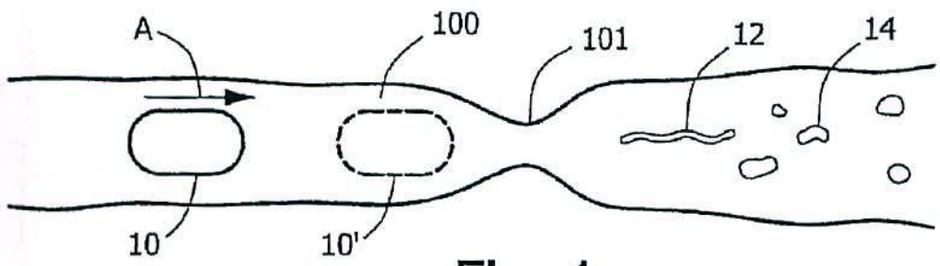


Fig. 1

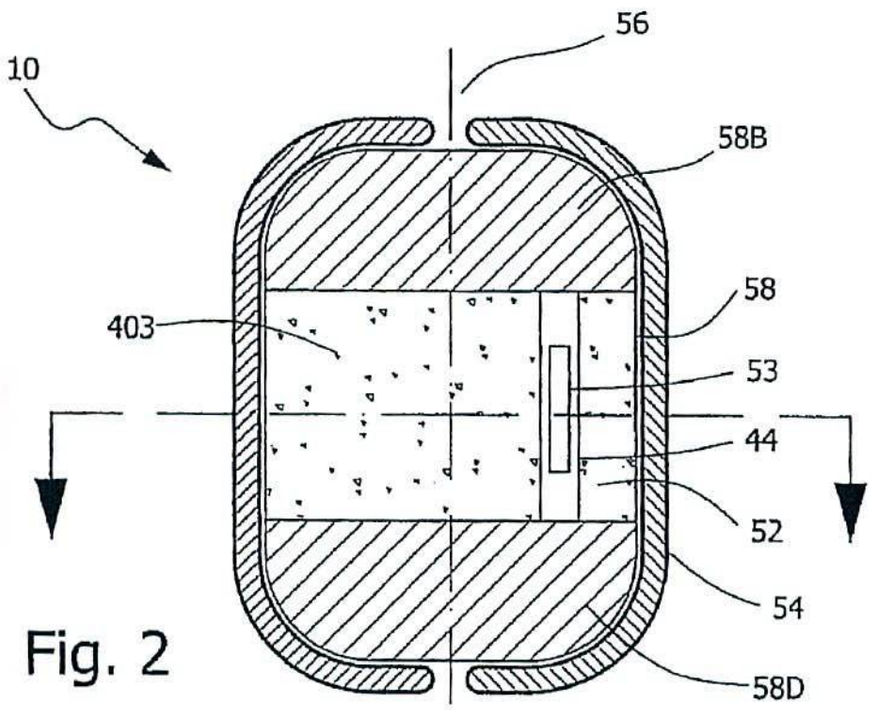


Fig. 2

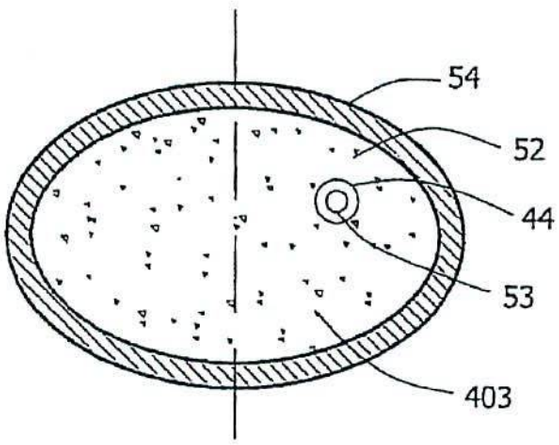


Fig. 3

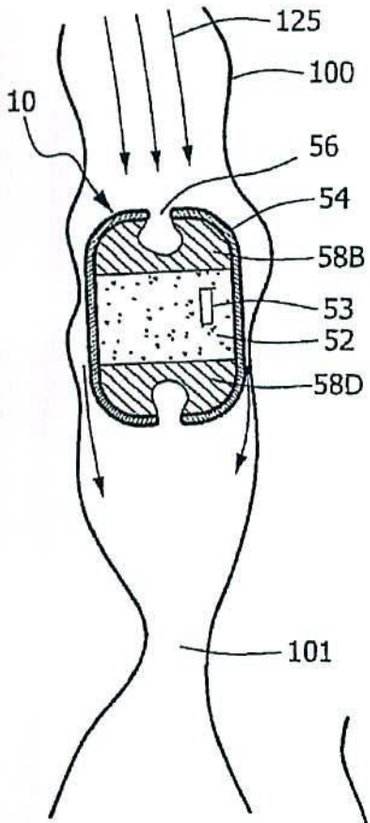


Fig. 4A

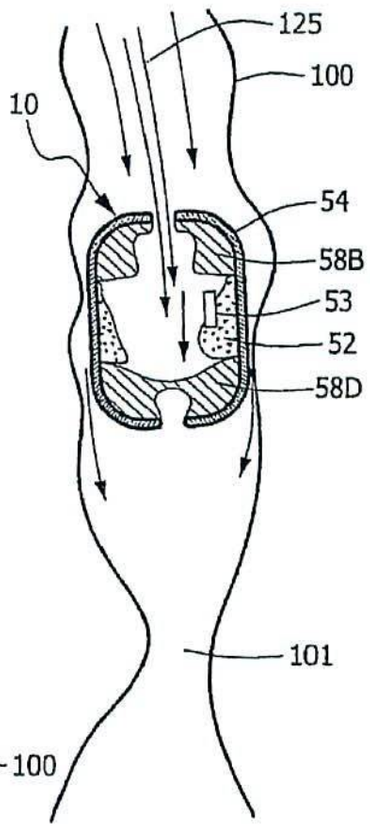


Fig. 4B

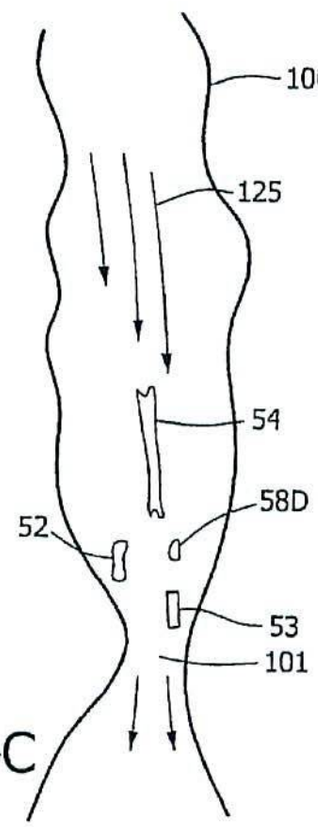


Fig. 4C

DEVICE AND METHOD FOR EXAMINING A BODY LUMEN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 10/192,861, entitled "Device and Method for Examining a Body Lumen", filed on Jul. 11, 2002 now U.S. Pat. No. 7,083,578, which is hereby incorporated by reference in its entirety, and which claims priority and benefit from (a) Israeli Patent Application Number 144296, entitled "A Device and Method for Testing a Body Lumen Configuration", filed on Jul. 12, 2001, which is hereby incorporated by reference in its entirety, and (b) Israeli Patent Application Number 147126, entitled "A Device and Method for Testing a Body Lumen Configuration", filed on Dec. 16, 2001, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to a device and method for examining a body lumen. The device and method may be useful, inter alia, in detecting abnormalities in a body lumen configuration.

BACKGROUND OF THE INVENTION

Tubular organs in the body may have a convoluted cavity configuration. The gastrointestinal tract, for example, starts from the oral cavity and proceeds through the esophagus, stomach, duodenum and small intestine, which may be a long tube that may fold many times to fit inside the abdomen. The small intestine is connected to the large intestine, which begins with the cecum, a small saclike evagination, then continues with the ascending colon, transverse colon, descending colon and the sigmoid (S-shaped) colon to the rectum. These body lumens may suffer from pathologies, which may affect the anatomy or configuration of the lumen. For example, strictures, narrowing or closure of a normally configured lumen may be caused by calcification or by the presence of scar tissue or a tumor. Strictures of the esophagus may be a common complication of chronic gastroesophageal reflux disease (GERD). Acute, complete obstruction of the esophagus may occur when food may be lodged in the esophageal stricture. Endoscopy may usually be employed to retrieve the food and relieve the obstruction.

Methods for diagnosis of body lumens may usually be symptom related or invasive. Non-invasive techniques of diagnosing the gastrointestinal (GI) tract may include utilizing solid non-degradable ingestible autonomous electronic or magnetically marked capsules. These autonomous capsules may include capsules for measuring motility in the GI tract, gastric pH (such as the Heidelberg capsule) and in-vivo temperature (such as the CoreTemp™ capsule). Also, gastric transit may be measured by using biomagnetic measuring equipment such as a magnetically marked capsule, which is a solid non-degradable oral dosage form containing powdered magnetite encapsulated in silicone rubber (W. Weitschies, R. Kotitz, D. Cordin, L. Trahms, (1997), *J Pharm Sci*, 86:1218-1222). Such capsules may typically be propelled through the GI system by peristalsis. These non-invasive methods may enable reaching parts of the intestine, for example, distal parts of the small intestine aejunum and ileum) that may not be reachable by other methods. However, in rare cases of severe strictures in the GI tract, swallowing of a solid bolus (such as an electronic or magnetically marked capsule) may cause obstruction of the GI tract.

Non-invasive methods for detection of strictures, specifically in the GI tract, usually include x-ray series that may be based on intake of x-ray opaque (radio-opaque) material (barium sulphate, gastrographine, or others), for example a barium pill (solid bolus) that dissolves rapidly for testing strictures in the esophagus. The material may reside for some time on the walls of the GI tract, enabling examination of the x-ray images of the GI tract. This technique may have several drawbacks, namely, low detection rate and exposure to x-ray radiation.

In-vivo devices, pills, or other medical systems may need to pass through the GI tract. However, it may be difficult to predict if such devices, pills, or systems may achieve safe passage through the GI tract, short of actually attempting to pass the objects through the tract.

SUMMARY OF THE INVENTION

Various embodiments of the present invention may provide an examining device capable of being depleted omnidirectionally, for example to facilitate its passage through abnormal configuration of a body lumen and a method for omnidirectional depletion of the examining device. In some embodiments of the present invention the examining device may have initial dimensions for a predetermined time period and may take on final dimensions in-vivo after a predetermined time period. The final dimensions may be substantially reduced as compared to the initial dimensions. In some embodiments of the present invention the examining device may be a solid bolus substantially coated with a substantially impermeable outer coating. The solid bolus may contain one or more caps and a device body. The device body may, for example, contain filler. One or more openings in the coating may expose the bolus and/or cap to an in-vivo environment. According to an embodiment of the invention one or more of the caps may serve as a timer. The coating may be depleted of the bolus in-vivo and may be collapsed to final dimensions.

BRIEF DESCRIPTION OF THE FIGURES

The subject matter regarded as the invention is particularly pointed out and distinctly claimed in the concluding portion of the specification. The invention, however, both as to organization and method of operation, together with objects, features and advantages thereof, may best be understood by reference to the following detailed description when read with the accompanied drawings in which:

FIG. **1** is a schematic illustration of two phases of an examining device in-vivo, according to an embodiment of the present invention;

FIG. **2** is a schematic illustration of a front cross sectional view of an examining device according to an embodiment of the present invention;

FIG. **3** is a schematic illustration of a top cross sectional view of an examining device according to an embodiment of the present invention; and

FIGS. **4A**, **4B**, and **4C** are consecutive schematic illustrations of a progression of an examining device passing through a stricture of a body lumen according to embodiments of the present invention.

It will be appreciated that for simplicity and clarity of illustration, elements shown in the figures have not necessarily been drawn to scale. For example, the dimensions of some of the elements may be exaggerated relative to other elements for clarity. Further, where-considered appropriate, reference numerals may be repeated among the figures to indicate corresponding or analogous elements.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, various aspects of the present invention will be described. For purposes of explanation, specific configurations and details are set forth in order to provide a thorough understanding of the present invention. However, it will also be apparent to one skilled in the art that the present invention may be practiced without the specific details presented herein. Furthermore, well-known features may be omitted or simplified in order not to obscure the present invention.

An atypical passage of an object through a body lumen or symptoms appearing after the insertion of an object into a body lumen may be indicative of an abnormal configuration of the body lumen. An examining device according to embodiments of the invention, which may, for example, examine a body lumen and/or may be an indicator of the body lumen configuration, may be designed to be depleted from its contents in-vivo and thus be safely exited from the body, independently of the configuration of the body lumen. According to one embodiment the body lumen may be the gastrointestinal (GI) tract.

Reference is now made to FIG. **1** showing a schematic illustration of the two phases of an examining device in-vivo, according to an embodiment of the invention. An examining device **10**, for example, an autonomous device having initial dimensions may be inserted into a body lumen **100** and may be moved through the body lumen **100** (for example, in the direction indicated by the arrow A) actively or passively. The device **10**, with initial dimensions, for example, a diameter of 1-12 mm may, for example, pass freely through the lumen **100** that may span over a given width, for example, a width of 1 mm to 10 cm, until a stricture **101** may be reached. Device **10** may pass through other body lumens and may have other suitable initial dimensions. At and/or near the stricture **101**, the width may decrease such that device **10** in its initial dimensions may not be able to pass through stricture **101**. In one example, stricture **101** may be a residual functioning lumen of, for example, about 2-10 mm. Strictures with other dimensions and other ranges of dimensions may be encountered by device **10**. The device (now illustrated in a broken line and referred to by the numeral **10'**) may be unable to continue its passage through the body lumen **100** due to its dimensions, which may be larger than the dimensions of the body lumen at the stricture **101**. The device **10**, in its initial dimensions, may thus be blocked at the stricture **101**. In some embodiments of the present invention, examining device **10** may block the opening through stricture **101**. Prolonged blockage of a body lumen, for example a body lumen of the GI tract may be dangerous and/or may cause discomfort to a patient.

After a predetermined time period the device's **10** dimensions may be changed, for example, to reduce or substantially reduce its dimensions and/or volume. Typically, the predetermined time period may be set to exceed the time period that it would normally take the examining device **10** to exit the body and/or specified body lumen in a case where no strictures were encountered. In some embodiments of the present invention, the device may change its dimension in a step-like fashion after the predetermined time period so as to avoid blocking a body lumen for a prolonged period. For example, for a predetermined time period, the device **10** may substantially maintain its initial dimensions and rigidity and soon after that predetermined time period the device may take on its final dimensions. In one example, the device **10** may be depleted from its contents and thereby, for example, collapse resulting in its final dimensions **12**. Omnidirectional depletion may facilitate clearing of the blockage that may be aggravated by device **10** in a near step-like fashion. In some embodiments of the present invention, depletion may take about 10-20 hours, for example 16 hours. In other embodiments of the invention, depletion may occur in a shorter or longer period of time. Final dimensions **12** may have, for example, a reduced volume and a flattened shape with a diameter substantially between 30 μm-100 mm. Other suitable ranges of final dimensions and shapes may result. In another example, device **10** may be, for example, disintegrate or degrade into several small sections or particles **14**, each of which may be approximately less than, for example, 0.5 wide. Other suitable ranges of final dimensions may be implemented that may be more or less than 0.5 wide. In other embodiments of the present invention device **10** may have final dimensions that may be any combination of final dimensions **12** and **14**. The device in its final dimensions **12** and/or **14** may pass through the stricture **101** and may, for example, exit the body. In alternate embodiments, the dimensions or shape of the body lumen **100** may be different and the device **10** may change in other manners, to other dimensions or shapes. For example, the device need not be broken into more than one section.

In another embodiment of the invention, the examining device **10** may be used to simulate the passage of another in-vivo device, such as a diagnostic and/or therapeutic device, through a body lumen, for example, an autonomous diagnostic and/or therapeutic device. In this case, obtaining information on the passage of the examining device through the body lumen may be advantageous in designing a specific in-vivo device or in determining whether a certain in-vivo device may be safely used on a patient. In one embodiment, different sized and shaped examining devices **10** according to an embodiment of the invention may be passed through a body lumen to determine the most suitable size and shape for an in-vivo device to be freely and safely passed through the same lumen.

In one embodiment of the present invention, the initial dimensions may be typically determined in accordance with the known anatomy and/or physiology of a body lumen. In its final phase the dimensions of the examining device may be typically substantially smaller and its shape possibly changed such that it may freely pass through the body lumen even if the lumen dimensions may be smaller than expected in accordance with the known anatomy and/or physiology of the body lumen. Proceeding from an initial phase to a final phase of the examining device, may, for example, be promoted by endoluminal conditions or may be externally controlled.

Passing of the examining device through a body lumen may, for example, simulate the passage of the target in-vivo device through that body lumen and thus a safe method of indication may be provided as to the transferability of the target in-vivo device in the body lumen.

Typically the examining device **10** may include at least two phases, an initial phase in which the examining device's (**10**) dimensions approximately resemble the dimensions of a target in-vivo device and a final phase in which the dimensions of the examining device **10** may be changed so as to enable the examining device **10** to pass through unexpected configurations of body lumen and/or abnormally configured body lumens. In other embodiments more than two phases may be implemented. In some embodiments of the present invention, the dimensions of examining device **10** may be changed, by depleting part and/or all of internal contents of the examining device **10** and changing the dimensions of an external portion of the examining device **10** to final dimensions.

In another embodiment of the present invention, the device **10** may be shaped, sized or have dimensions substantially similar to an autonomous ingestible imaging device for purposes of imaging the GI tract The device **10** may be safely passed through the GI tract, to test the transferability of such a diagnostic or therapeutic device through the GI tract, while its progression may be monitored and/or the phase the device **10** is in may be detected as may be described herein. In the event the device **10** may not traverse a section of the lumen, its shape or dimensions may change to allow passage. The examining device **10** may be, for example, capsule shaped, shaped similar to and containing components similar to the ingestible capsule described in U.S. Pat. No. 5,604,531, entitled "An in-vivo video camera system" which is hereby incorporated in its entirety by reference, Publication Number WO 01/65995, also assigned to the common assignee of the present application and incorporated herein by reference, and/or similar in shape and size to other pills, tables capsules and the like, known in the art.

In one embodiment, a capsule shaped examining device **10** possibly having, for example, initial dimensions of approximately 11 mm×26 mm may be used to test the GI tract. Other suitable dimensions may be used. The device **10** may be swallowed or otherwise placed or inserted in the GI tract (by an endoscope, for example) and may be passively moved through the GI tract due to peristalsis of the GI tract, until it may be naturally excreted from the body. In other embodiments of the present invention, device **10** may be actively advanced through the GI tract.

Reference is now made to FIG. **2** schematically illustrating a front cross sectional view of an examining device according to some embodiments of the present invention. According to an embodiment of the present invention, device **10** may be a bolus **58** capable of being disintegrated that may typically include a device body with, for example, filler **52** sandwiched between two caps **58**B and **58**D that may be substantially enclosed within a coating **54**, for example a pliable coating. In other embodiments of the present invention, more or less than two caps **58**B and **58**D may be used and filler **52** may not be sandwiched between two caps **58**B and **58**D. The coating **54** may typically be a layer or a plurality of layers of, for example, substantially impermeable or slightly permeable material or combination of materials, which may be essentially durable (e.g., may not corrode or disintegrate) under in-vivo conditions. The bolus **58** may typically be composed and/or fabricated from an eroding and/or dissolvable material. One or more openings, aperture, and/or windows **56** in coating **54** may partially expose bolus **58** to the surrounding environment and may allow, for example, in-vivo fluids to cause disintegration (e.g. erosion) of the caps **58**B and **58**D and depletion of device **10** over a predefined time period. Typically, an opening may be for example a circular opening with a diameter of approximately 1-10 mm and an area of approximately 0.5 to 100 mm^2. Other suitable openings with other shapes and sizes may be used as well. Erosion of caps **58**B and **58**D may be dependant on parameters, such as, the size of window **56**, the number of windows **56**, the direction that each window **56** faces with respect to the body lumen through which device **10** may be traveling, the properties of the material fabricating caps **58**B and **58**D, the dimensions and/or volume of the caps **58**B and **58**D, and the density of caps **58**B and **58**D. Other conditions may influence the erosion time of each of the caps **58**B and **58**D and the depletion time of device **10**. The caps **58**B and **58**D may be designed to erode at a desired predetermined time period. For example, the dimensions, material, and density of the material packaged may be set to meet the requirement of maintaining the external dimensions of the examining device **10** for a predetermined time period and subsequent to the elapsed predetermined time period, depleting the contents of the examining device **10** in a near step-like fashion. Typically, caps **58**B and **58**D may act as a timer for the disintegration of device **10**. More than one aperture and/or more than one window **56** facing in more than one-direction, for example substantially opposite directions, may allow bidirectional or omni-directional depletion of device **10**.

According to an embodiment of the invention, coating **54** has initial dimensions that are changeable to final dimensions and the bolus **58** comprises particles that are of final dimensions. Final dimensions enable passage of the device in a body lumen configuration that is not enabled by the initial dimensions. Partial or full depletion of coating **54** from bolus **58** may initiate the changes in the dimension of coating **54**. For example a volume that coating **54** encloses may be directly related to the volume of bolus **58** that coating **54** encompasses. Upon depletion of the contents encompassed by coating **54**, the initial dimensions of coating **54** may change to final dimensions in a near step-like fashion. The pliable characteristic of coating **54** may enable coating **54** to take on final dimensions that are substantially reduced form the initial dimensions. As such, coating **54** may pass through a stricture body lumen while intact.

In some embodiments of the present invention, a monitoring mechanism, for example, an ID tag **53** may be included within examining device **10**, for example, to allow monitoring of the presence of device **10** in a specified location and/or in-vivo. In other embodiments of the present invention, a traceable material **403**, for example a radio opaque material may be used to monitor the presence of examining device **10** in a specified location and/or in-vivo. In yet other embodiments, other suitable methods or a combination of more than one method maybe used to monitor device **10**. In other embodiments of the present invention, device **10** need not be monitored.

In one embodiment of the present invention, caps **58**B and **58**D may typically be fabricated and/or composed from a hydrophobic material, for example, a hydrophobic wax containing microencapsulated hydrophobic material, or from a combination of hydrophobic and hydrophilic material. Non-limiting examples of materials that may be suitable for cap **58**B and **58**D may, for example, include, Compritol 888, Avicel PH 200, Lactose anhydr., PVP K-90, or a combination of more than one material may be used. In another embodiment of the present invention, the cap may be composed and/or fabricated from other synthetic waxes or, for example, lipophilic material of plant origin or hydrocarbons (simple and/or complex). Other suitable materials may be used. According to one embodiment of the present invention, the hydrophobic material may include micro-particles to facilitate flow of in-vivo fluids into the cap and to facilitate the disintegration of the cap at a given rate. A system that may be suitable to use in an embodiment of the present invention may be a system of nano-particles, for example, formed of a solid hydrophobic inner core and a cationic exterior. The nano-particles may be encapsulated in micro-capsules. In one embodiment the nano-particles may be encapsulated In moisture sensitive micro-capsules. Such systems may be produced, for example, by Salvona, USA. In some embodiments of the present invention, caps **58**B and **58**D may be pressed into a desired shape and dimensions by known methods. Fabricating caps **58**B and **58**D by pressing of synthetic material, e.g. Compritol 888, Avicel PH 200, Lactose anhydr., and/or PVP K-90, may result in less or no expanding or swelling of the cap when coming in contact with in-vivo

fluids that may otherwise occur when using natural waxes or derivatives of natural waxes. In some embodiments of the present invention, the cap may be composed by a combination of hydrophobic and hydrophilic material and the ratio between the hydrophobic and hydrophilic material may determine and/or be related to the erosion rate of the cap. For example, a composition with a relatively higher ratio of hydrophobic material as compared to hydrophilic material, e.g. 1:3 hydrophobic/hydrophilic, may erode at a slower rate compared to a composition with a relatively lower ratio of hydrophobic material as compared to hydrophilic material, e.g. 1:12 hydrophobic/hydrophilic. In one example, the cap may be fabricated from layers of more than one or more than one combination of hydrophobic materials. In another example the cap may be fabricated from layers of material packaged with different densities. For example, to maintain the outer dimensions of the examining device intact for the predetermined time period, an outer layer of the cap may, for example, be pressed and/or packaged with a higher density than the internal layers so that erosion rate of in the inner portion of the cap may be higher than the erosion rate in the outer surface of the cap. Other suitable methods of fabricating caps **58**B and **58**D and/or eroding caps **58**B and **58**D while maintaining the outer dimensions of device **10** for a predetermined time period may be used. Typically but not necessarily, one or more caps **58**B and **58**D may have substantially similar dimensions. In some embodiments of the invention, one or more caps **58**B and **58**D may have different dimensions and/or configuration. In one embodiment of the present invention, in a device of about 11 mm×26 mm, caps **58**B and **58**D may have a substantially dome shape with a longitudinal length of approximately 4-6 mm. Other suitable sizes may be used and each of the caps **58**B and **58**D may have a different length or geometry. Typically, but not necessarily cap **58**B and **58**D and device body and/or filler **52** may be made of different materials.

Filler **52** may typically be of any suitable biodegradable or dissolvable material, for example any suitable excipient, e.g. lactose, powdered sugar, etc. Typically, filler **52** may be strong enough to withstand endo-luminal pressure. The filler **52** may also contain adhesives and other fillers to, for example, further provide mechanical stability to the device. Other suitable materials may be used. Filler **52** may be pressed into a desired shape and dimensions by known methods. In one embodiment of the present invention, filler **52** may be cylindrical with dimensions approximating 12-14 mm in length and 9-12 mm in diameter. Other suitable dimensions may be used. Caps **58**B and **58**D may be joined and/or glued to filler **52** with an adhesive, for example, a biocompatible adhesive, e.g. UV glue. Other suitable methods of joining caps **58**B and **58**D to filler **52** may be used. In other examples cap **58**B and **58**D may be joined and/or affixed to filler **52** by packaging and/or coating, for example, coating with coating **54**. Other suitable methods may be used

Typically, the outer coating **54** may be a thinner layer than the internal bolus **58**. According to some embodiments, the outer coating **54** may be designed to impart mechanical strength to the device and keep the device shape and dimensions constant throughout the initial phase (and/or the predetermined period) of the device. The coating may also serve as a barrier between the internal filler **52** and the surrounding environment, e.g. the endo-luminal environment. Typically, coating **54** may be a thin layer of impermeable polymer, for example, a thin layer of Parylene C, for example, an 8-10 μm layer of Parylene C. Other suitable coatings and coating methods may be used. Typically, upon depletion of bolus **58** through window **56**, coating **54**, which may be pliable, may change to final dimensions (e.g. reduced and/or collapsed dimensions). In some embodiments of the invention, coating **54** may collapse to final dimensions including a width of, for example, 30 μm-0.5 mm.

In one embodiment of the present invention, device **10** may also include a monitoring mechanism, for example, an ID tag **53** e.g. radioactive, color or magnetic tag or an electronic ID tag (e.g., an RFID tag) within the bolus **58** or filler **52**. Other monitoring mechanisms or beacon device may be used. ID tag **53** may be, for example, a radio-frequency (RF) ID tag. In one embodiment of the invention, the tag may include two components: a metal coil which may act as a two-way antenna and a silicon chip that may be activated by energy received from an outside source, and when activated may send back a single identification signal which may be picked up by an external pick up device, for example a radio frequency scanner. Typically, these components may be encapsulated in, for example, a glass casing. In one example, the glass casing may be re-encapsulated with for example medical grade polyurethane as a protective jacket. Other suitable methods for detecting the presence of the examining device may be implemented and other suitable ID tags **53** may be used. One exemplary dimension of an ID tag **53** may be 2-3 mm in diameter and 12-15 mm in length. Other suitable dimensions may be used.

Reference is now made to FIG. **3** showing a top cross sectional schematic illustration of device **10** where an ID tag **53** may be included in filler **52**. In one embodiment of the present invention, a bore **44** may be made within filler **52** so that an ID tag **53** may be inserted through it. In one embodiment of the present invention, bore **44** may have dimensions of 2 mm in diameter and 13 mm in length. Other suitable dimensions may be used. Other suitable methods may be used for incorporating an ID tag within device **10**.

In some embodiments of the present invention, a material **403** providing, for example, a radio opaque effect may be included within bolus **58**, e.g. within filler **52**. An example of a suitable material may be for example barium sulphate powder. Other suitable materials may be mixed into the filling for easily monitoring of device **10** by, for example, x-ray. In one embodiment of the present invention filler **52** may contain 10% barium sulphate powder. Other suitable concentrations and other suitable detectable materials may be used. The device **10** with ID tag **53** or traceable material **403** may be monitored, for example, by using a reader such as a suitable reader provided by Trovan Ltd. UK. Other methods of monitoring may be implemented. The tag may be the tags described herein, such as a radioactive marker, a magnetic device, or a radio based tag.

In one embodiment of the present invention, the device **10** may also include an examining mechanism, such as a thermometer, pH meter, etc., for examining endo-luminal conditions, or other sensing devices such as an imaging device. In another embodiment of the present invention, filler **52** may contain one or more medical drugs, for example, that may be released, for example in an abnormally configured lumen during depletion of filler **52**. In some embodiments of the present invention, an effervescent component may be added to filler **52** to expedite the depletion of filler **52**.

Device **10** may be designed to substantially maintain its outer dimensions for a predetermined period of time after which surface erosion through window **56** due to in-vivo fluids, for example, gastric and/or GI fluids may disintegrate and/or erode the caps **58**B and **58**D and the in-vivo fluids may penetrate the body of device **10** where they dissolve the filler **52**, leaving behind the pliable coating and the tag **53**. In some

embodiments of the present invention, the change in dimension may occur in a near step-like fashion.

In some embodiments of the present invention, the rate of erosion of caps **58**B and **58**D through windows **56** may not be uniform. In one example, device **10** may block the stricture **101** and little or no fluid may come in contact with the downstream facing cap **58**D. The exposure to in-vivo fluids on the downstream side of the device **10** may be significantly reduced such that, for example, erosion of cap **58**D may come to a near halt. In other embodiments of the present invention, exposure of each of the caps **58**B and **58**D may differ due to other conditions. Omnidirectional exposure to in-vivo fluid may ensure depletion of device **10** after a predetermined period elapsed and may accelerate the depletion of device **10** after the predetermined period elapsed. For example, exposure of in-vivo fluids may in general be greater for a cap **58**B facing upstream as compared to another cap **58**D facing downstream. In other embodiments of the present invention, non-uniform erosion of each of the caps **58**B and **58**D may be due to other factors, for example, each of caps **58**B and **58**D may be fabricated and/or composed with different materials, in different sizes, and/or shapes so that they may erode over different time periods. In yet other embodiments of the present invention, erosion of caps **58**B and **58**D may be due to other factors besides and/or in addition to exposure to in-vivo fluids.

In a method according to an embodiment of the present invention an examining device may examine endo-luminal conditions, or test the configuration of a body lumen, detect configurational abnormalities in a body lumen and/or simulate the passage of an in-vivo device in a body lumen while no long term obstruction of the body lumen may be posed. According to an embodiment of the invention, an examining device in its initial phase may include dimensions such that it may pass through a typically healthy body lumen and/or give a good approximation of the passage of an in-vivo device in the body lumen. In its final phase the examining device's dimensions may be changed (typically reduced, although other changes are contemplated) so that it may pass through an abnormally configured body lumen where the examining device in its initial phase could not, because of its dimensions.

In case the body lumen is of unexpected dimensions (wherein the expected dimensions are based, for example on the known or typical anatomy and/or physiology of the body lumen) or in case of a stricture or any other configurational abnormality in the body lumen, the examining device in its initial dimensions may be blocked from continuing its typical or expected passage in the body lumen. After a predetermined time the examining device's dimensions may be changed such that the examining device, in its final phase, typically depleted of its former contents and typically of degraded or reduced form, will not be blocked from passing even through a smaller or abnormally configured body lumen.

If no clinical or configurational abnormalities are present in the body lumen the examining device's passage through the body lumen may be typical and the examining device may pass through the body lumen and exits the body while it may still maintain its initial dimensions. However, in a case in which the body lumen may be abnormally configured (e.g., there is a stricture) or if there is a clinical problem (e.g., slow or no motility in the gastro intestinal tract) the examining device may be held back in the body lumen and reaches its final dimensions while in the body lumen. The degraded or reduced device may be able to continue its passage through the body lumen to eventually exit the body. It will thus be appreciated that the device and method of the invention may be utilized to detect clinical and/or configurational abnormalities in body lumens through which the device may be passed and exited, such as the GI tract, the urogenital tract, the reproductive tract, the oral-nasal cavity, etc, or a portion of any of these lumens.

A person skilled in the art may easily adjust the specific design of the examining device and the predetermined time period between an initial and final phase of the examining device to be applicable to a specific body lumen having specific and known anatomy and physiology.

Reference is now made to FIG. **4**A, **4**B and **4**C showing consecutive schematic illustrations of a progression of an examining device **10** passing through a stricture **101** of a body lumen **100** according to an embodiment of the present invention. Reference is now made to FIG. **4**A showing a front cross sectional schematic illustration of an examining device **10** traveling through body lumen **100** and approaching an area with a stricture **101**. During travel through body lumen **100**, contact with in-vivo fluids **125** through windows **56** may promote erosion of caps **58**B and **58**D. For a predetermined period, the erosion of caps **58**B and **58**D and/or the omnidirectional depletion of device **10** may continue with out compromising the rigidity and outer dimensions of device **10**.

In some embodiments of the present invention, erosion of caps **58**B and **58**D may be a function on the degree of contact caps **58**B and **58**D may have with the surrounding in-vivo fluids. For example, the orientation of examining device **10** with respect to the body lumen may result in one of its caps, for example cap **58**B, having greater exposure to in-vivo fluids as compared to another of its cap **58**D. For example, a first cap **58**B facing an upstream direction may have more exposure to in-vivo fluids as compared to second cap **58**D facing in a downstream direction. As such, the first cap **58**B facing in the upstream direction may erode within a shorter time period as compared to the second cap **58**D facing the downstream direction. Including two or more caps **58**B and **58**D in device **10** may, in some embodiments of the present invention, ensure that a desired change in dimension may take place at a predetermined time period, even if one of the caps **58**B or **58**D may have had insufficient exposure to in-vivo fluids due to in-vivo conditions. Omnidirectional depletion of device **10** may allow for accelerated depletion of device **10** and/or coating **54**, typically, in a step-like fashion at the termination of the predetermined period.

In another example, when approaching an area with a stricture, device **10** may, for example, block passage of in-vivo fluid and one of the caps, for example cap **58**D possibly facing the direction of the stricture may experience little or no contact with in-vivo fluids. As such, it may be possible that the erosion of caps **58**D may be temporarily halted, nearly halted, and/or slowed down. Omnidirection depletion of coating **54** enables the passage of device **10** regardless of the orientation of device **10** with respect to the body lumen **100** and/or regardless of the orientation of device **10** with respect to the stricture **101**.

Reference is now made to FIG. **4**B, showing a device **10** with a substantially eroded cap **58**B. In-vivo fluids may diffuse or flow in through window **56**, eroding, for example, cap **58**B enough to create an opening to filler **52**. The filler **52** may typically be made of a material that may be faster to dissolve than the material composing the cap **58**B and **58**D. Exposure of filler **52** to in-vivo fluids, may facilitate rapid depletion of filler **52** such that dimensions of device **10** may be substantially altered. In some embodiments of the present invention, filler **52** may be substantially dissolved before cap **58**D may have substantially eroded. As such, in-vivo fluids may expose cap **58**D through the filler **52** side and erosion of cap **58**D may occur from both sides, accelerating the erosion of cap **58**D, so

that device **10** may successfully pass through stricture **101** and relieve blockage that may have been temporarily aggravated by device **10**. In one embodiment of the present invention, erosion of cap **58**D may occur mainly from the upstream direction due to lack of in-vivo fluids in the downstream direction. In other embodiments of the present invention, device **10** may be able to pass through stricture **101** during depletion of filler **52** and before complete erosion of cap **58**D.

Reference is now made to FIG. **4**C. Erosion of cap **58**B, filler **52** and cap **58**D may, for example, lead to pliable coating **54** disengaging at least partially from the material that it may be coating and in its new smaller and/or collapsed dimensions may pass easily through stricture **101**. ID tag **53** may be released from filler **52** and also pass through stricture **101**. In other embodiments, fragments of filler **52** and caps **58**B and **58**D may pass through stricture **101** while still in the process of disintegration and/or erosion. In some embodiments of the present invention, rapid depletion of device **10** (after the predetermined time period may have elapsed) may be desired so as to minimize any discomfort to a patient (for example, undergoing an examination with examining device **10**) that may be caused by further blockage of a strictured area **101** by the examining device **10**. Erosion of caps **58**B and **58**D from both the upstream and downstream direction may accelerate the change in dimension of examining device **10** so that it may vacate the pathological and/or strictured area without unnecessary delay.

A health professional may monitor (e.g. with known monitoring devices) the passage of device **10** through a body lumen to determine the presence of abnormal body lumen configurations. The presence of device **10** or the contents of device **10** (e.g. ID tag **53**, material **403**) in-vivo for less than the predetermined time may be indication that no abnormal body lumen configurations were encountered. Detection of device **10** or the contents of device **10** (e.g. ID tag **53**, material **403**) in-vivo substantially after the predetermined time may be indication that abnormal body lumen configurations were encountered. In some embodiments of the present invention the predetermined time period may be in the order of one hundred hours. In other embodiments a period of approximately forty to seventy hours may be used. In still alternate embodiments, other time limits may be used, and examining devices for other body lumens may be designed in accordance with the specific body lumen having specific and known anatomy and physiology.

In one embodiment of the present invention, a health professional may detect the presence of device **10** in a defined area in a body lumen to determine the presence of abnormal body lumen configurations. The presence of device **10** or the contents of device **10** (e.g. ID tag **53**, material **403**) in a defined area for less than the predetermined time may be indication that no abnormal body lumen configurations were encountered. The presence of device **10** or the contents of device **10** (e.g. ID tag **53**, material **403**) in a defined area for more than the predetermined time may be indication that abnormal body lumen configurations were encountered.

The foregoing description of the embodiments of the invention has been presented for the purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed. It should be appreciated by persons skilled in the art that many modifications, variations, substitutions, changes, and equivalents are possible in light of the above teaching. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

The invention claimed is:

1. An in vivo examining device comprising:
- a device body;
- two erodible caps;
- a substantially impermeable outer coating for substantially covering at least the two caps, said coating comprising at least two openings, wherein each of said two caps is exposed by at least one of said two openings;
- wherein the device body is covered by the coating and comprises filler sandwiched between the two caps.

2. The device according to claim **1** wherein the caps include a combination of hydrophobic and hydrophilic materials.

3. The device according to claim **2** wherein the hydrophobic material is selected from a group consisting of: glyceryl behenate and microcrystalline cellulose, and the hydrophilic material is selected from a group consisting of: anhydrous lactose and polyvinylpyrrolidone.

4. The device according to claim **1** wherein the coating is durable under in-vivo conditions.

5. The device according to claim **1** wherein the coating is a pliable coating.

6. The device according to claim **1** wherein the coating includes Parylene C.

7. The device according to claim **1** wherein the coating is configured for taking on substantially reduced dimensions in-vivo after a predetermined time period.

8. The device according to claim **1** wherein the filler includes at least a dissolvable material.

9. The device according to claim **1** wherein the filler includes at least one material selected from a group consisting of: lactose and powdered sugar.

10. The device according to claim **1** wherein the device body comprises a monitoring mechanism.

11. The device according to claim **10** wherein the device body comprises an RF ID tag.

12. The device according to claim **1** wherein the device body includes at least barium sulphate.

13. The device according to claim **1** wherein each of the two caps is glued to the device body.

14. The device according to claim **13** wherein each of the two caps is glued to the device body with UV glue.

15. The device according to claim **1** comprising a monitoring mechanism.

16. The device according to claim **15** comprising an RF ID tag.

17. The device according to claim **1** wherein the device includes barium sulphate.

18. The device according to claim **1** wherein the area of each of the openings is 0.5 mm^2 to 100 mm^2.

19. A method of use of an examining device within a body lumen, the method comprising:
- providing an examining device with a body comprising a dissolvable filler material and two erodible caps, the examining device configured for being depleted omni-directionally after a predetermined time period; and
- inserting said examining device into said body lumen;
- wherein the dimension of said examining device changes to final dimensions after the predetermined time period in a step-like fashion, wherein final dimensions of the device include a width of between 30 μm and 0.5 mm.

20. The method according to claim **19** wherein the body lumen is a lumen of a GI tract.

21. The method according to claim 19 wherein the examining device is capsule shaped.

22. The method according to claim 19 comprising coating the examining device with a substantially impermeable outer coating.

23. The method according to claim 21 comprising providing an opening through the coating to expose the cap.

24. The method according to claim 21 comprising providing a first opening through the coating facing an upstream direction;

a second opening through the coating facing a downstream direction.

25. The method according to claim 19 comprising depleting the examining device in the upstream and downstream direction.

26. The method according to claim 19 wherein the predetermined time period is approximately between forty and one hundred hours.

27. The method according to claim 19 comprising monitoring the examining device.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,585,283 B2
APPLICATION NO. : 10/988614
DATED : September 8, 2009
INVENTOR(S) : Kraizer et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1230 days.

Signed and Sealed this

Fourteenth Day of September, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

120


US007807195B2

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

(10) **Patent No.: US 7,807,195 B2**
(45) **Date of Patent: Oct. 5, 2010**

(54) **EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1155 days.

(21) Appl. No.: **11/031,266**

(22) Filed: **Jan. 7, 2005**

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(30) **Foreign Application Priority Data**

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Sep. 13, 2004 (IN) 980/MUM/2004

(51) **Int. Cl.**
A61K 9/64 (2006.01)
A61K 9/52 (2006.01)
A61K 9/20 (2006.01)

(52) **U.S. Cl.** **424/458**; 424/456; 424/457

(58) **Field of Classification Search** 424/457
See application file for complete search history.

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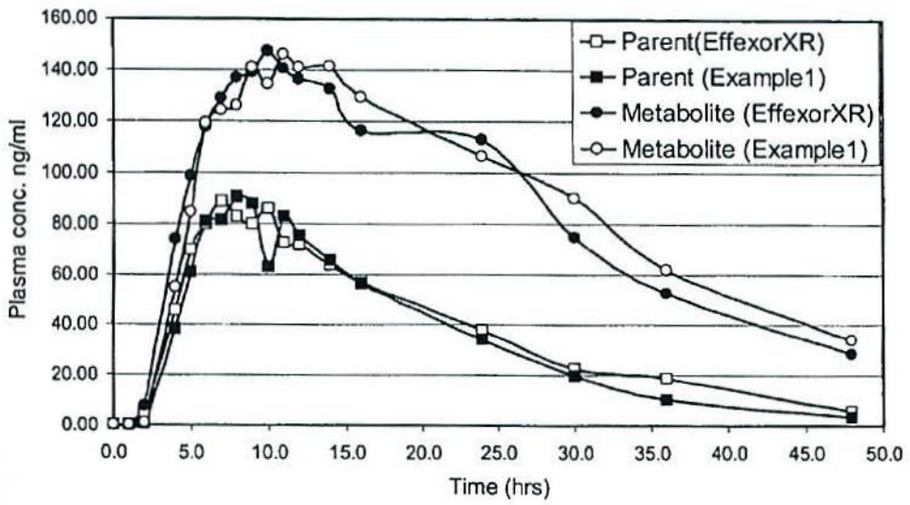
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Primary Examiner—Lakshmi S Channavajjala
Assistant Examiner—Rachael E Welter
(74) *Attorney, Agent, or Firm*—Akerman Senterfitt; Peter A. Chiabotti

(57) **ABSTRACT**

The present invention relates to an extended release once daily pharmaceutical formulation comprising venlafaxine hydrochloride and pharmaceutically acceptable excipients. More particularly, the present invention relates to an extended release composition in the form of mini-tablets which are incorporated in hard gelatin capsules.

3 Claims, 1 Drawing Sheet



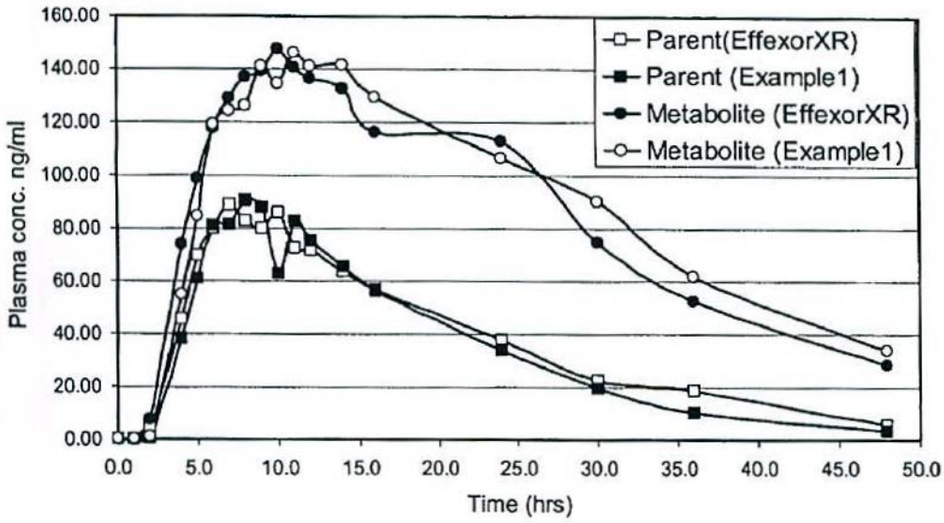

160.00
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Plasma conc. ng/ml
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
45.0
50.0
Time (hrs)
Parent(EffexorXR)
Parent (Example1)
Metabolite (EffexorXR)
Metabolite (Example1)

Fig. 1

EXTENDED RELEASE FORMULATION OF VENLAFAXINE HYDROCHLORIDE

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a pharmaceutical composition of extended release formulation comprising hard gelatin capsule containing therapeutically effective amount of mini-tablets wherein each mini-tablet comprises venlafaxine hydrochloride, microcrystalline cellulose, binder and optionally conventional excipients.

2. Related Art of the Invention

The use of hydrophobic polymers to produce extended or controlled release pharmaceutical composition is known in the art. For extending the release, the solid dosage form of mini-tablets comprising a drug is coated with hydrophobic polymer and pore forming agent. As soon as solid dosage form comes in contact with surrounding media, the pores are formed and the drug is diffused through these pores. Control of the rate of release benefits therapy by producing constant blood plasma levels of the active ingredient and by decreasing the frequency of administration, thereby improving patient compliance to the dosage regimen. The present invention provides a pharmaceutical composition of extended release capsule containing mini-tablets of venlafaxine hydrochloride suitable for once daily administration to human subjects.

The invention relates to an extended release pharmaceutical formulation for once daily administration, in particular to a controlled release pharmaceutical formulation of venlafaxine hydrochloride.

Several extended release drug delivery system adapted for the delivery of venlafaxine hydrochloride are known in the prior art.

U.S. Pat. No. 4,535,186 describes a class of hydroxycycloalkanephenethyl amines as being useful antidepressants and exemplifies the compound now known as venlafaxine hydrochloride as one of the suitable species.

Venlafaxine, is chemically named as (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]-cyclohexanol. Presently venlafaxine hydrochloride is administered to adults as conventional immediate release tablets or as 24 hours extended-release multiparticulate capsules. Venlafaxine hydrochloride is approved for sale in various countries including the United States of America under the brand name EFFEXOR™ (Wyeth Ayerst). It is available as an immediate release tablet and as an extended release capsule under the brand name EFFEXOR™ (Wyeth Ayerst) and EFFEXOR XR™ (Wyeth Ayerst), respectively.

Venlafaxine hydrochloride is very soluble in water. It is known that it is very difficult to develop a pharmaceutical form with a very slow dissolution rate of freely soluble drug.

U.S. Pat. No. 6,274,171 and related EP 0797991 disclose encapsulated extended release formulations form venlafaxine hydrochloride. A once daily, encapsulated extended release dosage form is disclosed that provides a flattened drug plasma profile and reduces the adverse side effects. The encapsulated dosage form is taught to comprise spheroids of venlafaxine hydrochloride, microcrystalline cellulose, and hydroxypropylmethylcellulose (HPMC). These spheroids are coated with a mixture of ethyl cellulose and HPMC. By providing an appropriate amount of the coating, the desired blood plasma profile can be obtained.

U.S. Pat. No. 6,274,171 and EP 0797991 also state that forming an extended release dosage from of venlafaxine hydrochloride was difficult in part due to the high water solubility of the hydrochloride salt. In fact, these patents

disclose that "[n]umerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies." Unlike the encapsulated extended release formulations described in these patents, a hydrogel extended release venlafaxine hydrochloride tablet is taught to typically exhibit a dissolution profile wherein 40%-50% is released within 2 hours, 60%-70% is released within 4 hours, and 85%-100% is released within 8 hours.

WO99/22724 also discloses encapsulated venlafaxine hydrochloride extended release dosage forms. These formulations differ from those in U.S. Pat. No. 6,274,171 and EP 0797991 in that the spheroid is substantially free of HPMC.

Although a venlafaxine extended release capsule has been produced, it would be advantageous to provide a less complicated dosage form that nonetheless provides extended release of venlafaxine.

WO94/27589 and WO01/37815 describe osmotic dosage forms containing venlafaxine hydrochloride.

US 20030190354 discloses an extended release composition comprising as active compound venlafaxine hydrochloride in a matrix tablet dosage form, in which venlafaxine hydrochloride is mixed with a combination of hydrophilic and hydrophobic matrix forming components. The matrix components are suitably combination of high and low viscosity grades hydroxyl propyl methyl cellulose, ethyl cellulose, glyceryl behenate and methyl cellulose. Two granulation methods were used for the production of the tablets: the first was a regular one step granulation process, in which all excipients were blended together with the active, then wet granulated with Kollidon SR, dried, milled and compressed into oval shape scored tablets. The second granulation process was a two step process, the first was wet granulation of the active material, which was blended with the hydrophobic components selected from Ethocel or Compritol. Later on, the milled granulate was mixed with the hydrophilic components, the methocels and the lubricating components, syloid 244 and Mg stearate.

WO03/55475 teaches the controlled release formulation of venlafaxine. The pharmaceutical formulation of the present invention comprises for example a core consisting of an active drug which may be advantageously in amorphous form, polyvinylpyrrolidone, a combination of two hydrophilic polymers having different viscosity and optionally other commonly used ingredients for solid dosage forms. The core is coated with a polymeric coating comprising a combination of two polymers having different water permeability. A plasticizer and other commonly used ingredients for film coating may be optionally added thereto. The combination of the carriers i.e. the water soluble polymer, polyvinylpyrrolidone and the low viscosity hydrophilic polymer has a double effect and the advantage that it stabilizes the amorphous form of the active ingredient and simultaneously modifies the release of the amorphous active ingredient in such a way that it is sustained, repeatable and independent of the amorphous or polymorphous form of the active ingredient, its particle size and specific surface area.

WO 03/53402 and related US 2004133982 discloses zero-order sustained release dosage forms. A solid dosage form comprising a matrix core comprising intragranular ethylcellulose and a water soluble active agent granulated and compressed together with extragranular ethyl cellulose and a film coating comprising a hydrophobic polymer wherein the film coating completely encases the matrix core. This invention also relates to a process for manufacturing a zero-order sus-

tained release tablet containing a water-soluble active agent, comprising the steps of: (a) preparing a first admixture comprising the active agent and intragranular ethylcellulose; (b) granulating the first admixture in order to obtain a granular product; (c) preparing a second admixture comprising extragranular ethylcellulose; (d) preparing a third admixture comprising the granular product and the second admixture;

WO04/12699 and related US 20040096501 teach the use of dual retard technique to effectively control the release rate of modified release active ingredient by using small quantity of release controlling agents. This dual retard technique thus sufficiently reduces the size of the dosage form, which is convenient for swallowing. The dosage form comprises of a) Micro matrix particles containing high solubility active ingredient and one or more hydrophobic release controlling agent, b) Coating of Micro matrix particles with one or more hydrophobic release controlling agents.

Extended release preparation of drugs are advantageous in the administration because of their reduced dosage frequency. The frequency can be reduced by maintaining constant plasma concentration of drug over an extended period of time to ensure extended effect of active ingredient.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an extended release of the active ingredient from the pharmaceutical composition, which has blood plasma levels above minimum therapeutic concentration over extended period of time.

Another object of the present invention is to provide extended release pharmaceutical composition for once daily dosage form.

Yet another object of the present invention is to provide an extended release pharmaceutical composition, which releases the active ingredient in predetermined manner.

Yet another object of the present invention is to produce the formulation by a conventional method so as to reduce the process time.

Yet another object of the present invention is to develop extended release formulation of venlafaxine hydrochloride which is bioequivalent to Effexor XR by conventional method comprising compression and coating.

Accordingly, the present invention relates to an extended release pharmaceutical formulation comprising venlafaxine hydrochloride, diluent, water-soluble component and water insoluble polymer and other pharmaceutical acceptable excipients.

The components are selected in such a way to give extended release of the venlafaxine hydrochloride in a predetermined manner.

The invention relates to extended release composition in the form of mini-tablets which are incorporated in hard gelatin capsules containing a therapeutically effective amount of the mini-tablets comprised of venlafaxine hydrochloride, microcrystalline cellulose, polyvinyl pyrrolidone and optionally conventional excipients and further coating of mini-tablets comprising of ethyl cellulose and plasdone S630 copolyvidonium (ISP technologies). The tablets of the invention exhibit specific dissolution profiles, especially with venlafaxine HCl.

Preferably, the present invention relates to the extended release formulation which comprises from about 40% to about 80% by weight of a venlafaxine hydrochloride; from about 25% to about 45% of microcrystalline cellulose and from about 0.5% to about 10% polyvinyl pyrrolidone of the total weight of composition. The coating on mini-tablet comprises of from about 2% to 15% of total weight of the composition. The coating composition comprises from about 50% to about 95% ethylcellulose and from about 3% to about 50% of plasdone S-630 copolyvidonium (ISP technologies) of the total weight of the coating layer.

More preferably the present invention relates to the extended release formulation which comprises from about 48% to about 68% by weight of a venlafaxine hydrochloride; from about 26% to about 38% of microcrystalline cellulose and from about 2% to about 9% of polyvinyl pyrrolidone of the total weight of composition. The coating on mini-tablet comprises of from about 4% to 14% of total weight of the composition. The coating on mini-tablet comprises of from about 65% to about 95% ethylcellulose and from about 5% to about 40% of plasdone S-630 copolyvidonium of the total weight of the coating layer.

Still more preferably the present invention relates to the extended release formulation which comprises from about 57% to about 62% by weight of a venlafaxine hydrochloride; from about 27% to about 32% of microcrystalline cellulose and from about 2.5% to about 5.5% of polyvinyl pyrrolidone of the total weight of composition. The coating on mini-tablet comprises of from about 6% to 12% of total weight of the composition. The coating on mini-tablet comprises of from about 70% to about 80% ethylcellulose and from about 20% to about 30% of plasdone S-630 copolyvidonium of the total weight of the coating layer.

BRIEF DESCRIPTION OF THE INVENTION

According to the present invention, the extended release formulation is prepared by compression followed by functional coating method, the said method comprising steps of:

i. Blending the venlafaxine hydrochloride and diluent.
ii. Granulating the blended mixture with an aqueous or non-aqueous solution of binder and drying it.
iii. Lubricating the dried granules and compressing into tablets of appropriate shape (3-6 mm in diameter).
iv. Coating the tablets with an aqueous or non-aqueous dispersion of water insoluble and water soluble polymer.
v. Filling coated mini tablets obtained in step (iv) into capsule of appropriate size.

Such 12, 6, 3 mini-tablets are filled into pharmaceutically acceptable capsule to form 150 mg, 75 mg and 37.5 mg strengths respectively of venlafaxine.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plot of the mean drug plasma level resulting from the biopharmaceutical test comparing Example 1 to venlafaxine hydrochloride 150 mg (Effexor XR™), of which the pharmacokinetic parameters are recorded in Table 1.

DETAILED DESCRIPTION OF THE INVENTION

In an embodiment of the present invention, the hard gelatin capsule comprises of film coated mini-tablets. These mini-tablets comprised of active ingredient, binder and water-soluble component and optionally conventional excipients. These mini-tablets are coated with combination of water-soluble and waters insoluble polymer.

According to the present invention, the pharmaceutical composition contains venlafaxine hydrochloride as an active ingredient. The venlafaxine hydrochloride may be present in an amount from about 40% to about 80%, preferably from

about 48% to about 68% by weight, more preferably from about 57% to about 62% of the total weight of extended release composition.

Further, venlafaxine hydrochloride may be present in an amount from 12.5 mg to 400 mg per capsule.

According to the embodiment of the present invention, the mini-tablet contains microcrystalline cellulose as diluent. Microcrystalline cellulose may be present in an amount from about 25% to about 45%, preferably from about 26% to about 38% by weight, more preferably from about 27% to about 32% of the total weight of extended release composition.

According to the embodiment of the present invention, the mini-tablet contains polyvinyl pyrrolidone as binder. Polyvinyl pyrrolidone may be present in an amount from about 0.5% to about 10%, preferably from about 2% to about 9% by weight, more preferably from about 2.5% to about 5.5% of the total weight of extended release composition.

In addition to the above ingredients, pharmaceutical grade magnesium stearate/stearic acid as a glidant, talc as an anti-adherent and colloidal silicion dioxide as a lubricant are included in the mini-tablet. Preferably, magnesium stearate/stearic acid, talc and colloidal silicion dioxide are present in amounts in the range of 1% to 6% by weight either alone or in combination.

In an embodiment of the present invention, the coating on mini-tablet comprises of water insoluble polymer and water-soluble polymer. The water insoluble polymer is selected from the group consisting of cellulose ether such as ethylcellulose, a cellulose ester such as cellulose acetate, methacrylic derivatives available from Rohm Pharma under the trade name "Eudragit™" RL, RS and NE, etc. In a preferred embodiment, the water insoluble polymer is ethyl cellulose present in an amount from about 50% to about 95% by weight of the functional coating content of extended release composition.

In an embodiment of the present invention, the coating on mini-tablet also contains water-soluble polymer. The water soluble polymer is selected from the group consisting of Plasdone S-630 copolyvidonum (ISP technologies), hydrated colloidal silica, sucrose, mannitol or any other substance capable of playing the same role. In preferred embodiment, the water soluble polymer is Plasdone S-630 copolyvidonum (ISP technologies) which is present in an amount from about 3% to about 50% by weight of the functional coating content of extended release composition.

Ethyl cellulose, an ethyl ether of cellulose, is a long-chain polymer of b-anhydroglucose units joined together by acetal linkages. It is tasteless, free flowing, white to light tan colored powder. It is a stable, slightly hygroscopic material. It is practically insoluble in glycerin, propylene glycol and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate and tetrahydrofuran and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxy groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol and toluene. It is chemically resistant to alkalis, both dilute and concentrated and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethyl cellulose polymers exhibit good stability within the pH range of 3 to 11, so they can be used with both acidic and alkaline ingredients.

The viscosity of ethyl cellulose is measured typically at 25° C. using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene: 20% ethanol (w/w). Different grades of ethylcellulose are ethocel std 4 premium, ethocel std 7FP premium, ethocel std 7 premium, ethocel std 10FP premium, ethocel std 10P premium, ethocel std 20P premium, ethocel std 45P premium, ethocel std 100FP premium, ethocel 100P having viscosity range of 3-5.5 cP, 6-8 cP, 6-8 cP, 9-11 cP, 9-11 cP, 18-22 cP, 41-49 cP, 90-110 cP, 90-110 cP respectively. The viscosity of an ethylcellulose solution increases with an increase in ethylcellulose concentration. The viscosity of such solutions depends almost entirely on the alcohol content and is independent of toluene. In addition, nonpharmaceutical grades of ethylcellulose that differ in their ethoxyl content and degree of polymerization are available. Ethyl cellulose is prepared by treating purified cellulose with an alkaline solution, followed by ethylation of the alkali cellulose with chloroethane.

Plasdone S-630 copolyvidonum (ISP technologies) is a synthetic water-soluble copolymer consisting of N-vinyl-2-pyrrolidone and vinyl acetate in a random 60:40 ratio. Plasdone S-630 copolyvidonum has low hygroscopicity. At 50% RH level, Plasdone S-630 copolyvidonum gains less than 10% weight and does easily desorb the gained moisture. It is an excipient of choice for moisture sensitive drugs.

The K-value for Plasdone S-630 copolyvidonum is specified between 25.4 and 34.2. The K-value is calculated from the kinematic viscosity of a 1% aqueous solution and hence is related to the average molecular weight of the polymer.

Plasdone S-630 copolyvidonum is a highly effective film forming adhesive. It is used primarily as a tablet binder, although its unique properties make it useful in the formulation and coating of a variety of pharmaceutical dosage forms.

Plasdone S-630 copolyvidonum is soluble in many solvents and can be used in non-aqueous granulation or coatings. It is supplied as a free-flowing spray-dried powder to ensure maximum handling efficiency. Spray drying results in spherical particles with tightly controlled particle size distribution. The particle morphology is responsible for the excellent powder flow properties, which aids blending with other excipients.

According to a process for making the composition of the present invention, the venlafaxine hydrochloride is blended with microcrystalline cellulose and granulated using binder solution. These granules are then compressed into mini-tablets. The resulting mini-tablets are then coated with extended release polymer.

In an embodiment of the present invention, the functional coating is done by dissolving ethylcellulose and plasdone S 630 copolyvidonum in a solvent such as ethyl alcohol. The resulting solution is sprayed onto the mini-tablet cores, using a coating pan or a perforated turbine or a fluidized bed apparatus.

In an embodiment of the present invention, the weight ratio of functional coating/tablet is comprised e.g. between 0.02 and 0.15, preferably between 0.04 and 0.14, more preferably between 0.06 and 0.12.

The mini-tablet size ranges between 3-6 mm in diameter.

Preferably, venlafaxine hydrochloride and diluent are sifted through suitable mesh sieve and the sifted mass is blended using high shear mixture and the blended mass is granulated with aqueous or non-aqueous binder solution and the granulated mass is dried until the moisture content is less than 4% w/w and the dried mass is passed through suitable mesh sieve and this granules are lubricated with lubricants, glidants, antiadherants. The lubricated granules are compressed into mini-tablets of appropriate size (3-6 mm in diameter). The mini-tablets are further coated with coating of water soluble and water insoluble polymer. These film-coated mini-tablets are filled into hard gelatin capsule.

The present invention is illustrated by the following examples.

EXAMPLES

General Procedure for the Preparation of Extended Release Capsule Containing Mini-Tablets

Venlafaxine hydrochloride and microcrystalline cellulose is sifted through suitable mesh sieve and the sifted mass is blended using high shear mixture and the blended mass is granulated with aqueous polyvinyl pyrrolidone solution and the granulated mass is dried until the moisture content comes down to less than 4% w/w and the dried mass is passed through suitable mesh sieve and this granules are lubricated with magnesium stearate, colloidal silicon dioxide and talc and the lubricated granules are compressed into mini-tablets.

These mini-tablets are coated with aqueous or non-aqueous dispersion of functional coating of water soluble and water insoluble polymer. The diameter of film-coated mini-tablet ranges between 3-6 mm. These mini-tablets are then filled into hard gelatin capsule.

Such 12, 6, 3 mini-tablets are filled into pharmaceutically acceptable capsule to form 150 mg, 75 mg and 37.5 mg strengths respectively of venlafaxine hydrochloride.

Dissolution Method

For all examples, the capsule containing tablets were tested for dissolution of venlafaxine hydrochloride in 900 ml of water as dissolution media at 37° C. and in 40-mesh basket (USP Type 1) and rotated at 100 rpm.

In the following examples, the composition and its dissolution profiles are given in a tabular form.

Example 1

Composition

Ingredient	Weight (mg/tablet)
Venlafaxine HCl	14.27
Microcrystalline Cellulose	7.13
Povidone	1.10
Ethyl Alcohol	q.s
Talc	0.25
Colloidal Silicon Dioxide	0.25
Magnesium Stearate	0.50
Ethyl Cellulose	1.22
Copolyvidone	0.37
Ethyl Alcohol	q.s.
Total Weight	25.09

Dissolution Profile

Time (hour)	Percent Venlafaxine HCl released
1	0
2	13
4	38
8	62
12	75
24	92

Example 2

Composition

Ingredient	Weight (mg/tablet)
Venlafaxine HCl	14.27
Microcrystalline cellulose	7.13
Povidone	1.10
Pure Water	q.s.
Talc	0.25
Colloidal Silicon Dioxide	0.25
Magnesium Stearate	0.50
Ethyl Cellulose	1.59
Copolyvidone	0.48
Ethyl Alcohol	q.s.
Total Weight	25.57

Dissolution Profile

Time (hour)	Percent Venlafaxine HCl released
1	0.2
2	7.7
4	23.2
8	46.2
12	60
24	81.9

Example 3

Composition

Ingredient	Weight (mg/tablet)
Venlafaxine HCl	14.27
Microcrystalline cellulose	7.13
Povidone	1.10
Pure Water	q.s.
Talc	0.25
Colloidal Silicon Dioxide	0.25
Magnesium Stearate	0.50
Ethyl Cellulose	1.08
Copolyvidone	0.32
Ethyl Alcohol	q.s.
Total Weight	24.9

Dissolution Profile

Time (hour)	Percent Venlafaxine HCl released
1	6.2
2	22.7
4	48.8
8	77.5
12	92.2
24	102.7

Example 4

Composition

Ingredient	Weight (mg/tablet)
Venlafaxine HCl	14.27
Microcrystalline cellulose	7.13
Povidone	1.10
Pure Water	q.s.
Talc	0.25
Colloidal Silicon Dioxide	0.25
Magnesium Stearate	0.50
Eudragit RS 30D	3.15
Talc	0.16
Triethyl Citrate	0.19
Pure Water	q.s.
Total Weight	27.00

Dissolution Profile

Time (hour)	Percent Venlafaxine HCl released
1	8
2	9
4	12
8	85
12	104
24	—

Further, when the composition of the present invention was extruded, spheronized and dried to form spheroids instead of mini-tablets as envisaged in the present invention, the dissolution profile was more immediate, which is unsuitable for once daily administration, as shown in the accompanying example:

Example 5

Composition

Sr. No.	Ingredient	Qty/Capsule (150 gm)
	CORE	
1	Venlafaxine HCl	171.24
2	Microcrystalline Cellulose	85.56
3	Povidone	13.20
4	Water	q.s.
	COAT	270.00
8	Ethyl Cellulose	19.500
9	Copolyvidone	5.86
10	Ethyl Alcohol	q.s.
	TOTAL WEIGHT	295.36

A uniformly blended mixture of Venlafaxine Hydrochloride (171.24 g) and microcrystalline cellulose (85.56 g) was granulated into an over wetted dough using solution of povidone (13.2 g) in water. The plastic mass was extruded, spheronized and dried to prepare uncoated spheroids. The cylindrical extrudes of the composition were very sticky and fragile with variable length of the extruded cylinders which resulted into non-uniform spheroids during spheronization. The extrudes were difficult to spheronize. The formed spheroids were irregular shaped and excessively sticky in nature which resulted in the formation of aggregates. Aggregates were removed by sieving after drying the spheroids. The spheroids were further coated in a wurster type fluid bed coater with a solution of 19.5 g of Ethyl cellulose and 5.86 g of Copolyvidone in Ethyl alcohol. The fragile nature of the spheroids resulted in formation of too many fines while coating. The presence of fine bridged the formation of few aggregates during coating. The film coated spheroids were sieved to remove those aggregates and then filled into pharmaceutically acceptable capsules.

The in vitro drug dissolution studies were conducted on the formed spheroids using USP I at 37° C. and 100 rpm in 900 ml water. The drug release was as follows:

Time (Hours)	Percent Venlafaxine HCl released
1	21
2	84
4	99

The dissolution profile suggests that preparing spheroids of the composition claimed in the present invention would have a more immediate drug release characteristics unsuitable for once daily administration. The said invention is thus only workable for mini-tablets of diameter greater than 3 mm and not for spheroids of diameter less than 2 mm.

Biopharmaceutics:

A randomized, two treatment, two period, two sequence, single dose, crossover bioavailability study on Venlafaxine 150 mg extended release capsule (Example 1), compared with Venlafaxine hydrochloride 150 mg extended release capsule (Effexor XR™) manufactured by Wyeth Ayerst laboratories, USA, in 12 healthy, adult, male, human subjects was conducted under fasting conditions. The mean drug plasma level are shown in FIG. 1 and the pharmacokinetic parameters are recorded in Table 1.

TABLE 1

		Parent		Metabolite	
Parameter	Unit	Example 1	Effexor XR	Example 1	Effexor XR
Cmax	ng/mL	101.28	106.183	162.33	166.025
Tmax	h	7.67	8.500	11.25	12.17
AUC(0->t)	ng · h/mL	1560.62	1669.10	4119.86	3949.95
AUC(0->inf)	ng · h/mL	1635.48	1823.616	4740.36	4494.14

The invention claimed is:

1. An extended release formulation of venlafaxine hydrochloride in the form of compressed mini-tablets having a diameter of 3-6 mm, filled in a hard gelatin capsule, said mini-tablets having a core and an outer coating, the core of said mini-tablets comprising from about 57-62% of venlafaxine hydrochloride by weight of each mini-tablet, from about 27-32% of microcrystalline cellulose by weight of each mini-tablet, and from about 2.5-5.5% of polyvinylpyrrolidone by weight of each mini-tablet, and said coating comprising (i) 70-80% of a water insoluble polymer which is selected from ethylcellulose and copolymers comprising at least two monomers selected from the group consisting of acrylic acid, methacrylic acid, esters of acrylic acid, and esters of methacrylic

acid and 20-30% of a water soluble polymer which is copolyvidone, and (ii) 5-14% of the total weight of the mini-tablets, wherein said formulation exhibits the following dissolution profile when measured in a USP type I apparatus at 37° C. in water at 100 rpm:

a) at least 46.2% of total venlafaxine hydrochloride is released at 8 hrs;

b) at least 60% of total venlafaxine hydrochloride is released at 12 hrs; and

c) at least 81.9% of total venlafaxine hydrochloride is released at 24 hrs.

2. The extended release formulation of venlafaxine hydrochloride according to claim **1**, which is administered once daily.

3. The extended release formulation of venlafaxine according to claim **1**;

wherein the extended release formulation of venlafaxine hydrochloride is prepared by a process comprising the steps of:

(i) blending the venlafaxine hydrochloride and microcrystalline cellulose,

(ii) granulating the blended venlafaxine hydrochloride and microcrystalline cellulose with an aqueous or non-aqueous solution of polyvinylpyrrolidone and drying it to form dried granules,

(iii) lubricating the dried granules and compressing said granules into mini-tablets,

(iv) coating the mini-tablets with an aqueous or non-aqueous dispersion of a water insoluble component selected from ethylcellulose and copolymers comprising at least two monomers selected from the group consisting of acrylic acid, methacrylic acid, esters of acrylic acid, and esters of methacrylic acid and a water soluble component of copolyvidone, and

(v) filling coated mini-tablets obtained in step (iv) into capsules.

* * * * *


US007838027B2

(12) **United States Patent**
Venkata Ramana Rao et al.

(10) **Patent No.: US 7,838,027 B2**
(45) **Date of Patent: *Nov. 23, 2010**

(54) **PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS**

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This patent is subject to a terminal disclaimer.

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

Pantoprazole sodium multiparticulates are described which avoid sticking to nasogastric and gastronomy tubes. The pantoprazole multiparticulates have a spheroid core of pantoprazole or an enantiomer thereof, or a salt thereof, a surfactant, and a disintegrant; a sub coat which is comprised of hydroxypropyl methylcellulose (hypromellose) and water, an enteric coat on the sub-coat, and a final seal coat over the enteric coat, which is composed of hydroxypropyl methylcellulose (hypromellose) and water.

24 Claims, No Drawings

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PANTOPRAZOLE MULTIPARTICULATE FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a national stage application under 35 U.S.C. 371 of PCT/US04/033058, filed Sep. 30, 2004, which claims the benefit under 35 U.S.C. 119(e) of the priority of U.S. Patent Application No. 60/507,810, filed Oct. 1, 2003.

BACKGROUND OF THE INVENTION

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole, is a H+/K+-adenosine triphosphate (ATP) inhibitor (also known as acid pump or proton pump inhibitor (PPI), is an enzyme present in the gastric parietal cells. It is believed that these drugs are metabolized in the parietal cells to active sulfenamide metabolites that inactivate the sulfhydryl group of the proton pump, thus reducing the hydrogen ion secretion. PPIs are generally lipophilic weak bases with poor aqueous solubility at low pH. Many PPIs are unstable in low pH solutions and undergo rapid acid-catalyzed degradation, and they are relatively stable at neutral or high pH.

The current commercial oral formulations of sodium pantoprazole are single unit coated tablets. See, e.g., U.S. Pat. No. 5,997,903, which describes oral forms of pantoprazole that consist of a core, an intermediate layer and an outer layer. The current coating has a tendency to cause undesirable sticking of the tablet to the gastrointestinal tract.

Multiparticulate formulations, because of their nature of dispersing in the gastrointestinal tract, show a reduced food effect and variability in gastric emptying times, thereby providing for reduced inter and intra subject variability, as compared to single unit tablets (Intl. Journal of Pharmaceutics 140 [1996] 229-235).

Several unsuccessful attempts have been made in the past to develop a multiparticulate formulation of pantoprazole. However, these attempts yielded multiparticulates that were not bioequivalent to tablets, only 70% relative bioavailability was found. Another attempt using different technologies—non-pareil seed coating and extrusion/spheronization, resulted in a product that did not provide the appropriate release in acid conditions. In addition, these attempts yielded product that was unstable, as observed by discoloration, when stored at room temperature.

SUMMARY OF THE INVENTION

The invention provides a stable multiparticulate pantoprazole formulation that provides reduced inter and intra subject variability.

In one embodiment, the pantoprazole multiparticulates of the invention is composed of a spheroid core comprising pantoprazole or an enantiomer thereof, or a salt or hydrate thereof, at least one surfactant, at least one distintegrant, and about 1% to about 2% w/w water; an enteric coat on the core, said enteric coat comprising a copolymer of methacrylic acid and methacrylates in the range of about 15 to about 45% w/w of the spheroid core; wherein said multiparticulates have an average size of about 1 mm in diameter.

Advantageously, the multiparticulate formulations of the invention are stable under room temperature storage conditions for at least twelve months. Based on the trend analysis using the twelve month room temperature data and 6 month 40° C./75% relative humidity (RH) data available to date, the multiparticulates of the invention should have a shelf life of over 2 years. Typically, a multiparticulate formulation of the invention is considered stable if it retains 90% to 110% of its potency during shelf life storage.

This pantoprazole multiparticulate formulation of the invention is less prone to adherence to the intestinal walls, nasogastric and gastromy tubes, and pouch material thereby giving predictable delivery of the drug product to the site of drug release. It also provides for an early onset of action for relief of gastro-intestinal pain and has a prolonged duration of action. This formulation allows dosing to pediatric patients and patients who have difficulty swallowing solid foods. This formulation also allows for drug delivery via nasogastric and gastrostomy tubes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a multiparticulate formulation of pantoprazole having a unique combination of excipients and a surfactant (e.g., polysorbate 80) that are compatible with pantoprazole sodium in the presence of an alkaline pH environment. Further, the invention provides a process that utilizes low shear during granulation and low temperature during drying for preparation of the multiparticulate. This process contributes to the stability of the core of the multiparticulates of the invention.

In one aspect, the invention provides multiparticulate formulations of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, i.e., in the lower gastrointestinal tract.

The multi particulate formulation of sodium pantoprazole of the invention provides an enhanced system for the delivery of pantoprazole to patients. The current marketed formulation is a single monolithic tablet. The present formulation of multiparticulate spheroids, which is adaptable for use in a capsule or a foil packet, can be prepared by extrusion/spheronization plus coating technology.

The composition of the multiparticle of the invention, and the enteric coat, e.g., Eudragit, allows for reduced release at low pH (~1) and fast release at a neutral pH (~7). This provides faster blood levels of the drug, in patients, and thereby a faster onset of action. The smaller T_{lag} value of multiparticulate formulation as compared to that of a single monolithic tablet based on the results from dog data indicates faster onset of action of multiparticulate formulation.

The use of a multi particulate formulation facilitates dosing to pediatric patients and patients who have trouble swallowing, by dispersing the spheroids in a suspending liquid or sprinkling/dispersing in a low pH liquid like applesauce, prior to administration. The suspending liquid could be made prior to administration by mixing a blend of powder material with water. The smaller size of the multi particulates, in a capsule or pouch or any other container, also allows dosing through nasogastric or gastrostomy tube.

This formulation allows for a faster relief of GI pain, and prolonged duration of action (extended release), as compared to the current marketed tablet.

I. Multiparticulates of the Invention

Suitably, the multiparticles are in the range of about 0.1 to 2 mm, or 0.5 mm to 1.5 mm, or 0.7 mm to 1.25 mm, or 0.8 mm to 1 mm. In one embodiment, the multiparticulates in a composition of the invention average about 1 mm in diameter. Typically, the multiparticles of the invention are no greater than about 1 mm in size in order to facilitate passage through nasogastric tubes

The multiparticulates of the invention are composed, at a minimum, of a spheroid core with an enteric coat over the core. In between the core and enteric coat an initial seal coat may be applied, e.g., comprising a coating of hydroxylpropyl methylcellulose (hypromellose). Also, over the enteric coat a final seal coat may be applied, e.g., a coating of hydroxylpropyl methyl cellulose (hypromellose). The spheroid core is composed of, at a minimum, a pantoprazole or a salt thereof, and a surfactant.

As used herein unless the context requires otherwise, the term 'pantoprazole' refers to 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulphinyl]-1H-benzimidazole and enantiomers thereof and the term 'pantoprazole compound' includes pantoprazole and enantiomers and salts and hydrates thereof. The active compound, pantoprazole is described in European Patent 166 287, which describes the preparation thereof, and is available commercially under the brand name PROTONIX®. Examples of pharmaceutically acceptable salts of pantoprazole include, e.g., sodium, magnesium, and calcium, among others; still others are described in the European Patent 166 286, which is incorporated by reference herein. The selection of a suitable salt is not a limitation of the invention. In one embodiment, the salt is sodium. Typically, the pantoprazole compound is present in the range of from about 5 to 50% w/w, more preferably about 20 to 45% w/w, of the total multiparticulate.

Suitable surfactants are known to those of skill in the art. However, particularly desirable are sodium lauryl sulfate, polysorbates, including, e.g., polysorbate 80, and mixtures of these components. Typically, the surfactant is present in the core in an amount of about 2 to about 7% w/w, and desirably, about 5% w/w of the core. In another embodiment, the surfactant is present in a ratio of about 5:3 drug:surfactant (e.g., pantoprazole sodium sesquihydrate to sodium lauryl sulfate) to about 10:1 drug:surfactant (e.g., pantoprazole sodium sesquihydrate to polysorbate 80). Advantageously, the surfactants in the multiparticulate formulation have been found to enhance the wettability and, thus, the speed and extent of release and absorption of the sodium pantoprazole, from the multi particulate formulation of the invention.

The spheroid core can further contain a disintegrant, a pH adjuster and, optionally a binder or another excipient such as hydroxypropyl methylcellulose (e.g., hypromellose 2208). Suitably, the total amount of disintegrant(s) present in the core is an amount of about 15% w/w to about 80% w/w, or about 20% w/w to about 70% w/w, or about 25% w/w to about 45% w/w, or about 30% w/w to about 42% w/w. In one embodiment, the total amount of drug to binder is represented by a ratio of from about 50:1 to about 40:1 by weight drug: binder. The total amount of a pH adjuster in the formulation can range from about 0.1% w/w to about 10% w/w of the multiparticulate, or about 1% w/w to about 8% w/w, or about 3% w/w to about 7% w/w. However, these percentages can be adjusted as needed or desired by one of skill in the art.

The disintegrant may be selected from among other known disintegrants, including, e.g., cellulose, and crospovidone, among others. In one embodiment, the disintegrant is selected from among microcrystalline cellulose and crospovidone, and mixtures thereof. The binder may be selected from among known binders, including e.g., cellulose, and povidone, among others. In one embodiment, the binder is hydroxylpropyl methyl cellulose (hypromellose). Suitable pH adjusters include, e.g., sodium carbonate, sodium bicarbonate, potassium carbonate, lithium carbonate, among others. Still other suitable components will be readily apparent to one of skill in the art.

In one embodiment, the spheroid core contains, w/w based on the dry uncoated core, about 45% pantoprazole sodium sesquihydrate (about 40% free pantoprazole), about 25 to 30%, and preferably about 27% microcrystalline cellulose, about 4 to 6%, and preferably about 5% polysorbate 80, about 14 to 16%, and preferably about 15% crospovidone, about 0.5 to 2%, and preferably about 1% hypromellose 2208, about 5 to 8%, and preferably about 6.5% sodium carbonate. In one embodiment, the spheroid core contains:

pantoprazole sodium sesquihydrate	45.24% w/w
microcrystalline cellulose	27.25% w/w
polysorbate 80	5% w/w
crospovidone	15% w/w
hypromellose 2208	1% w/w
sodium carbonate	6.5% w/w

In another embodiment, the spheroid core contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573

Although moisture is removed from the core during the drying process which is described below, the core preferably retains about 1% to about 2% w/w water. Without wishing to be bound by theory, the inventors believe that this water content contributes the stability of this multiparticulate as compared to the failed prior art attempts at forming a multiparticulate pantoprazole.

Optionally, an initial seal coat (or subcoat) can be applied directly to the core prior to coating with the enteric coat. Although the components of this seal coat can be modified by one of skill in the art, a particularly suitable initial seal coat is composed of hydroxypropyl methylcellulose (hypromellose) and water. For example, a suitable initial seal coat can be applied as a 7.5% w/w hypromellose solution. Typically, such a seal coat is in the range of about 2% w/w to about 4% w/w of the uncoated core or about 1% w/w to about 2% w/w of the coated multiparticulate.

In one embodiment, a multiparticulate with a subcoat contains:

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
A. Sub Coat:	4.00 mg	1.943
Pantoprazole Sodium Pellets (40 mg pantoprazole per 100 mg pellets)	100.00 mg	48.573

-continued

Ingredients	Amount/ Capsule	% w/w, based on total weight multiparticulate
Hydroxypropylmethyl cellulose 2910, USP, 6 cps	4.00 mg	1.943
Purified water, USP/BP/EP *removed during processing	9.33 mg*	
Total	104.00 mg	50.516

The enteric coat is applied over the initial seal coat, if present, or directly to the uncoated spheroid core. Suitably, the enteric coat is applied such that it coats the core in an amount of about 15 to 45% w/w, or about 20% w/w to about 30% w/w, or about 25% W/W to 30% w/w of the multiparticulate. In one embodiment, the enteric coat is about 27.5 to 32.5% w/w of the multiparticulate. Suitably, the enteric coat contains a product which is a copolymer of methacrylic acid and methacrylates, such as the commercially available Eudragit L 30D-55. In one embodiment, the enteric coat is composed of a Eudragit L 30D-55 copolymer, talc, triethyl citrate, sodium hydroxide and water. More particularly, the enteric coating may contain about 30% w/w of multiparticulate (applied as a 30 wt % dispersion) of Eudragit L 30D-55 coating; about 15% W/W talc, about 3% triethyl citrate; a pH adjuster such as sodium hydroxide and water. Other suitable materials may be selected for use in the enteric coat including, e.g., hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate and the like.

In one embodiment, a multiparticulate of the invention is provided with a subcoat over the core and an enteric coat as follows:

Ingredients	Amount/capsule	% w/w, based on total weight multiparticulate
Core + Subcoat	100.20 mg	48.67
Eudragit L30D-55	208.00 mg 62.40 (solids)	30.309
Talc, USP, Altalc 500V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N solution	9.30 mg 0.36 (solids)	0.175
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP *removed during processing	183.38 mg*	
Total	204.20 mg	99.186

In one embodiment, the enteric-coated multiparticulate is further coated with a final seal coat. Suitably, this final seal coat is comprises hydroxypropyl methylcellulose, and about 0.1% w/w to 10% w/w of the coated multiparticle, 0.1% w/w to about 5% w/w, or about 0.2% w/w to about 4% w/w.

In one embodiment, a final seal coat of hydroxypropyl methylcellulose in an amount of 0.5 to 1% w/w of the multiparticulate in water (which is removed during processing) is applied over the enteric coat. Following this, a coating of talc can optionally be applied over the final seal coat, in an amount of about 0.05 w/w to about 1% w/w, and preferably 0.1% w/w to 0.5% w/w.

In one embodiment, the resulting multiparticulate formulation of the invention achieves a geometric mean AUC ratio of test/reference of 89 to 94 with a 90% confidence interval of 84 to 100 for the ratio or achieving a geometric mean Cmax ratio of test/reference of 62 to 66 with a 90% confidence interval of 56 to 74 for the ratio or an in-vitro dissolution profile as shown below:

		% Drug Release			
Media	Time	Initial	6 Months @ 25 C./ 60% RH	6 Months @ 40 C./ 75% RH	Target
Acid (pH 1.0)	2 hrs	0.33	0.45	0.6	NMT 10%
Followed by	3 min	—	0.91	0.85	—
Alkaline	6 min	—	3.61	1.83	—
Buffer	9 min	—	52.25	16.45	—
(pH 6.8)	12 min	—	89.65	75.15	—
	15 min	101.58	97.15	91.92	—
	30 min	105.29	100.67	98.96	—
	45 min	105.29	100.57	99.14	NLT 75%
	60 min	105.06	100.52	99.07	—

In another embodiment, the resulting multiparticulate formulation of the invention achieves a mean AUC of 5451 to 5629 ng·h/ml and mean Cmax of 1865 to 1929 ng/ml or an in-vitro dissolution profile as shown below:

	% Drug Release*			
	Acid	Buffer (min)		
Batch	2 hrs	15	30	45
Initial	0.08	101.77	107.44	107.38
6 Months @40 C./75% RH	0.73	95.44	101.12	101.21
12 Months @25 C./60% RH	0.30	96.11	101.92	102.20

*Specifications: Acid at 2 hrs - NMT 10.0%; Buffer at 45 min - NLT 75%

However, the invention is not limited to these exemplary profiles.

Without wishing to be bound by theory, it is believed that final seal coat layer of hydroxypropyl methylcellulose provides a physical barrier for reduced contact between the mucoadhesive Eudragit layer and the upper GI tract, and thereby allows the reliable transit of the multiparticulates to the proper pH environment in the GI tract for effective release and absorption of the drug. In addition, the final seal coat layer of hydroxypropyl methylcellulose imparts anti-sticking properties to the multiparticulates and thus the multiparticulates are not sticking to the pouch material and/or nasogastric tube. The multiparticulates of the invention are useful for administration via the nasogastric tube and via food vehicles, particularly acidic food vehicles.

II. Method of Producing Multiparticulate Formulations of Invention

In another aspect, the invention provides a method of producing the multiparticulate formulations of the invention.

Typically, the uncoated pantoprazole compounds are prepared are follows. The dry components, including, at least the pantoprazole compound and the binder are dry blended in a suitable mixer under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment,

with the rpm adjusted to the appropriate low shear settings for the selected equipment. Optionally, hydroxypropyl methylcellulose or crospovidone may be substituted or additionally included in this step. Additionally, a pH adjuster may be included in this step.

Subsequently, the liquid components, e.g., the surfactant and water, are mixed in to afford a granulated product by mixing under low shear conditions. Suitable low shear conditions can be readily achieved using, e.g., a Hobart mixer, at a range of about 25 rpm to 35 rpm, and most desirably, 32 rpm. However, one of skill in the art will be able to achieve comparable low shear conditions using different equipment, with the rpm adjusted to the appropriate low shear settings for the selected equipment. The granulation is then extruded and spheronized through a suitable device (e.g., a NICA extruder/spheronizer) and the resulting spheroids are dried, sifted, and optionally blended prior to storage.

The inventors have found that a significant advantage is provided to the stability of the compound when the multiparticulates of the invention are dried at low temperature. Desirably, the spheroid cores of the pantoprazole multiparticulates of the invention are dried to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%. As used herein, low temperature drying refers to a temperature not exceeding about 40° C. for a period of 10 to 12 hours. When the drying conditions exceed this temperature and time period, impurities are observed that contribute to instability. In one embodiment, drying of the core is performed in the range of 35° C. to 40° C., or about 37° C. to 39° C. for about 8 to 72 hours. In another embodiment, the core is dryed at about 40° C. for 10 to 12 hours. Suitably, when coating layers are applied as described, the drying temperature for the various coating layers is also in this range.

Optionally, an initial seal coat of a hydrophilic polymer can be applied to the uncoated multiparticulates. For example, an initial seal coat composed of hydroxypropyl methylcellulose and purified water can be applied on a fluid bed coater, e.g., by spraying.

The enteric coat can be applied directly to the uncoated spheroid core, i.e., the uncoated multiparticulate, or may be applied over an initial seal coat. The enteric coat as described above, is typically applied on a fluid bed wurster coater.

In one embodiment, a final seal coat is applied over the enteric coat and, optionally, talc is utilized in the final step prior to filling the multiparticulates into a suitable packaging unit.

The multiparticulate of the invention may be in any suitable form including, e.g., granules, pellets, beads, minitabs, sphelules, beadlets, microcapsules, millispheres, nonocapsules, microspheres, platelets, tablets, and capsules, depending upon the desired route of delivery.

III. Formulations, Kits and Methods of Delivery

In another embodiment, the present invention provides products containing the pantoprazole multiparticulates of the invention.

Suitably, the multiparticulate compositions of the invention are formulated such that a patient receives a suitable amount of the pantoprazole, e.g., 5 mg to 200 mg, about 10 mg to about 100 mg, or about 40 mg (measured based upon free pantoprazole). Preferably, the formulations are such that a suitable dose is delivered in a single dosage unit. These doses may be administered daily for a suitable period of time, e.g., 4 weeks to 8 weeks, but can be delivered for a shorter period of time, e.g., 3 days to 3 weeks, one week to 3 months, or over a longer period, e.g., over 6 months, or longer. These compositions can be delivered alone or in combination with an antacid or other suitable composition.

In one embodiment, the invention provides a method of treating humans by administering an effective dose of the pantoprazole multiparticulates such that an area under curve (AUC) at least bioequivalent to Protonix® 40 mg tablet and Cmax as listed in Table VI are achieved.

In one embodiment, the pantoprazole multiparticulates are packaged for use by the patient or his caregiver. For example, the multiparticulates can be packaged in a foil or other suitable package and is suitable for mixing into a food product (e.g., applesauce and other acidic food vehicles) or into a drink for consumption by the patient.

The pantoprazole multiparticulate formulations of the invention are useful for treatment of gastroesophageal reflux disease (GERD), ulcers of the stomach and duodenum, and Zollinger-Ellison Syndrome.

In another embodiment, the pantoprazole multiparticulates are suspended in a physiologically compatible suspending liquid.

In yet another embodiment, the pantoprazole multiparticulates are filled in capsules, caplets or the like for oral delivery.

In still a further embodiment, the invention provides method of treating a subject in need thereof by administering an effective dose of the pantoprazole multiparticles of the invention.

The following examples illustrate specific embodiments of the invention and are not a limitation on the present invention.

Example 1

Pantoprazole Sodium Multiparticulate Formulations

Using a NICA extruder/spheronizer, during initial formulation development, several prototypes of uncoated multiparticulates were manufactured to obtain a target immediate release profile similar to or faster than the pantoprazole sodium uncoated tablet, currently available as Protonix (20 mg and 40 mg) tablets. Levels of the disintegrant crospovidone from 5 to 28.5% and the binder hydroxypropyl methyl cellulose from 0.5 to 1% were evaluated during preparation of uncoated multiparticulates over four batches.

A. Preparation of Uncoated Pantoprazole Sodium Multiparticulates

More particularly, pantoprazole sodium sesquihydrate, microcrystalline cellulose, hydroxypropyl methylcellulose (hypromellose 2208), crospovidone and sodium carbonate are dry blended in a Hobart mixer. Thereafter, polysorbate 80, NF (vegetable source) and purified water, USP, are added to the Hobart mixer. The resulting granulated produce is extruded and spheronized in a NICA® extruder/spheronizer and the spheroids are tray dried at a temperature not beyond 40° C. and sifted, followed by transfer to a PK blender. The final spheroids are stored in drums.

One of the batches (an approximately 200 gm batch) with 15% disintegrant crospovidone and with 1% hydroxypropyl methylcellulose (Hypromellose 2208) was selected as a prototype with similar release profile. The sieve cut of the uncoated spheroids from this batch was between 500-1000 microns.

B. Prototype Lab Batch (Batch A)

Approximately 100 grams of these uncoated spheroids were coated in a 3" Wurster Fluid Bed coater with Eudragit L30D-55 and hypromellose to result in Enteric coated multiparticulates.

During coating for this batch, the level of hydroxypropyl methyl cellulose (HPMC) initial seal coat was 4% of the weight of the uncoated multiparticulates. The % w/w of the dry polymer Eudragit L30D-55 used was 22.16%. In the coating batch, talc was introduced as dry powder in the coating chamber instead of being a part of the suspension. This was due to the small nozzle size (0.5 mm) used for coating the 100 g batch, which could potentially be clogged. The percent of talc and triethyl citrate used for the lab batch was less as compared to the clinical batches which were subsequently prepared. The multiparticulates were hand filled into size #2 HPMC capsules at a fill weight of 206 mg. The capsules were tested in vitro in 0.1 N HCl and pH 6.8 phosphate buffer. Less than 1% was released in acid media in 2 hours and greater than 80% was released in basic media in 45 minutes as desired.

These capsules were tested in dogs. The C_{max} and AUC were compared against the current marketed Protonix 20 mg tablet (and values were extrapolated to the 40 mg strength). It was seen that these multiparticulates released drug at a much faster rate than the current Protonix tablet in pH 6.8 phosphate buffer as desired. The final seal coat comprises hydroxypropyl methylcellulose (hypromellose) and water. This batch was packaged as spheroids in clear glass vials and placed on stability at accelerated conditions (30° C./65% relative humidity (RH) and 40° C./75% RH). The stability was monitored for 3 months. The potency and dissolution results are presented in Table I. The multiparticulates were stable over the three month period and a 40 mg equivalent dose of multiparticulates filled into capsules at each stability time point met all dissolution and stability criteria

Dissolution was tested by filling the stored spheroids into capsule shells, and dissolving in 0.1 N HCl (target release at 2 hours: not more than (NMT) 10%), followed by dissolution in pH 6.8 phosphate buffer (target release at 45 min: not less than (NLT) 75%. The acceptance criteria further required a strength of 90 to 110% of the label claim.

TABLE I

Stability of multiparticulates in clear glass vials.

		Test		
			Dissolution - Percentage Released (avg)	
Unit	Time	Strength (HPLC) % Label	0.1 N HCl	Secondary dissolution in phosphate buffer
Initial		100.0%	0.9%	91.6%
Ambient Room Temp	1 month	97.2%	0.8%	88.5%
	7 month	108.5%	0.8%	94.1%
30° C./60% RH	1 month	99.3%	0.5%	83.4%
	2 month	98.3%	NA	NA
	3 month	104.4%	0.7%	82.2%
40° C./75% RH	1 month	95.4%	0.7%	86.1[1]
	2 month	97.3%	NA	NA
	3 month	102.7%	0.7%	89.4%

[1]One capsule - 78% released.

Example 2

Coated Pantoprazole Sodium Multiparticulate Formulations (Batch B)

Based upon the lab batch A, a further scale-up batch of 1400 g was manufactured using a 7" wurster fluid bed coater. During coating for this batch, the level of hydroxypropyl methyl cellulose initial seal coat was 2% of the weight of the uncoated multiparticulates as compared to 4% for the coated Batch A. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. Also, the talc was added directly to the coating suspension as a larger nozzle size (1 mm) was used.

Initial release of coated multiparticulates in 0.1 N acid was high (9.0%) and very close to the limit of 10%. This Batch (B) did not meet the stability and dissolution criteria when tested at accelerated conditions (30° C./60% relative humidity (RH) and 40° C./75% RH). Trial from this batch indicated that an initial seal coat of greater than 2% of uncoated multiparticulates enhances stability of the multiparticulates. Additionally, more enteric polymer loading may be beneficial to control the release in acid media as the process is scaled up.

Example 3

Preparation of Pantoprazole Multiparticulates Scale-Up Batch

A. Technical Batch

Using a NICA extruder/spheronizer, a 36 kg technical batch of uncoated multiparticulates was prepared and 20 kg of this batch were enteric coated in a Glatt GPCG-15 machine to result in a 32 kg batch of coated multiparticulates. The % w/w of the dry polymer, Eudragit L30D-55 used was 22.16% w/w. This batch was filled into size #3 HPMC capsules at a fill weight of 156 mg. The release in 0.1 N HCl at 2 hours was greater than the desired 10%. Based on this, taking into account scale-up effects, minor adjustments were made to the formula and process for clinical batch.

B. Clinical Batch

Two 12 kg sub batches of a wet granulated mass were extruded and spheronized on a NICA extruder/spheronizer resulting in wet multiparticulates. The multiparticulates were tray dried at 40° C. for 10 to 12 hours to the desired % LOD of 3.4% to 4.3%. The batch was screened and only 16 kg of uncoated multiparticulates were used for coating to ensure uniformity and completeness of coating in the GPCG-machine. The sieved uncoated multiparticulates were coated with an initial hydroxypropyl methycellulose seal coat, followed by an Eudragit L30D-55 enteric coat, followed by a hydroxypropyl methycellulose final coat to result in 33 kg of coated multiparticulates. This batch was filled into size #2 HPMC capsules at a fill weight of 206 mg.

The release in 0.1 N HCl at 2 hours was less than the 10% limit and in pH 6.8 phosphate buffer, it was greater than the 80% limit at 45 minutes. The batch met in vitro release characteristics. The one month stability date showed that the multiparticulates were stable at 40° C./75% RH for one month. Currently, this batch is stable up to one year at room temperature and up to 6 months at 40 deg. C./75% RH. Stability study at room temperature condition beyond one year is ongoing. The one year room temperature stability results of this batch are shown in the following Table II.

The spheroid filled capsule had a faster in vitro release (dissolution) as compared to the Protonix 40 mg tablet in pH 6.8 phosphate buffer.

TABLE II

Stability of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg

	Test						
	Appearance and Description	Strength (HPLC)	Water (KF)	Purity Specification		Dissolution	
	#2 Opaque white capsules (cap and body) containing white to off-white colored spheroids	90.0-110.0% Label Claim (LC)	For Information	Largest Single Known or Unknown Impurity ≤0.5 (RRT)	Total Known and Unknown Impurities ≤2.0	Dissolution in 0.1N HCl NMT 10% in 2 hrs. Conforms to USP <724>	Dissolution in Phosphate Buffer NLT 75% in 45 min. Conforms to USP <724>
		%	%	%	%	%	%
Initial	Conforms	100.3	5.1	BRL	BRL	0	105
Initial (Spheroids only)[a]						0	107
25° C./60% RH							
1 Month	No Change	99.5	5.2	0.17 (1.39)	0.17	1	103
2 Month	No Change	101.4	4.6	0.15 (1.38)[b]	0.23	0	101
3 Month	No Change	101.2	4.5	0.17 (1.39)	0.17	0	100
6 Month	No Change	101.3	4.5	0.18 (1.38)[b]	0.24	0	100
6 Month (Spheroids only)[a]						0	112
9 Months	No Change	99.2	5.1	0.21 (1.40)[b]	0.33	0	101
9 Months (Spheroids only)[a]						0	108
12 Months	No Change	99.1	5.1	0.08 (0.14)	0.23	0	102
12 Months (Spheroids only)[a]						0	104

BRL = Below Reporting Limit (0.05%).

NMT = Not more than.

NLT = Not less than.

RRT = Relative retention time.

[a]Initial and revalidation dissolution results are provided for Pantoprazole Sodium Spheroids, 40 mg/206 mg, which is the ingoing batch of spheroids used for manufacture of Pantoprazole Sodium Spheroid-filled Capsules, 40 mg.

[b]Corresponds to the impurity at RRT = 1.39.

Example 4

Evaluation of Batch A Formulation in Beagle Dogs

The in-vitro release data of the sodium pantoprazole multi particulate formulation shows a faster release than the current marketed tablet. This provides earlier absorption and thereby a faster onset of action. The dog data clearly shows earlier drug levels of sodium pantoprazole from multiparticulates as compared to the single monolithic tablets. Earlier onset of action provides faster relief from gastric pain and other gastrointestinal (GI) disorders.

Pantoprazole sodium formulations have been evaluated in Beagle Dogs (n=5). The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole is illustrated in the Table III below.

As illustrated, the non-optimized lab batch of sodium pantoprazole multiparticulate formulation dosed in dogs shows smaller lag time than the current marketed tablet. In the following table, AUC refers to the area under a curve plotting mean concentration against protocol time. C_{max} refers to the maximum observed concentration value in the blood sample after administration. T_{max} refers to the time point when C max occurs. T_{lag} refers to the time following administration before effective amounts of the drug are observed in the circulation; $t_{1/2}$ (hr) provides the half-life for drug elimination. Relative bioavailability compares the absorption of a product from the gut in comparison with a dose given intravenously (assumed 100%).

TABLE III

The mean (SD) pharmacokinetic parameters and relative bioavailability of pantoprazole

Parameter	20 mg Market Tablet Batch A Pantoprazole Na[a]	40 mg Multiparticulate Capsule Batch A with enteric coat - Pantoprazole Na
AUC (μg*hr/mL)	16.3 (2.46)	17.3 (2.33)
Cmax (μg/mL)	11.7 (3.55)	7.10 (1.76)
Tmax (hr)	1.70 (0.84)	1.20 (0.27)
tlag (hr)	1.10 (0.91)	0.25 (0.18)
t ½ (hr)	0.62 (0.17)	0.77 (0.21)
Relative Bioavailability	—	AUC: 106%[b] Cmax: 61%[b]

[a]AUC and Cmax are normalized to a 40 mg dose

[b]Relative to Market Product Tablet

The dog data of the sodium pantoprazole multi particulate formulation gives a similar AUC as the current marketed tablet. Without wishing to be bound by theory, it is believed that the faster release and similar AUC of the multi particulates is achieved by lowering the level of the disintegrating agent crospovidone (as compared to the level in the tablet) and incorporating the functional excipient polysorbate 80 in the core of the spheroids.

Example 5

Pantoprazole Sodium Sesquihydrate: Excipient Formulations

This study was performed to determine the compatibility of pantoprazole sodium sesquihydrate with hypromellose 2208, sodium lauryl sulfate (SLS), crospovidone, and polysorbate-80.

A. Study Design

The study consists of two sets of samples. The first set contained drug and excipient. The second set contained drug, excipient and approximately 2 μl water. The reason for the water along with the drug and the excipient is to see whether additional water present causes any incompatibility.

The excipients were mixed with the drug in the ratio indicated in the following table. The excipients and the drug were weighed into a glass vial. Then the vials were vortexed for 15 seconds. Similarly, a second set of samples was prepared. Approximately 2 μl (the smallest amount of water that can be added with the pipette in the lab) was added to these vials. Then the vials were vortexed for 5 seconds. Finally, the first and second set of vials were capped and placed in stability chambers. The conditions tested were 40°/75% RH and 51° C. for 3 weeks.

B. Results

The results of this drug-excipient compatibility study are presented as % recovery in the Table IV below. The selection criteria for the compatibility or incompatibility are based on the % recovery between 90-110%.

TABLE IV

Drug: Excipient Compatibility Results

Excipient	Ratio of Drug:Excipient	% Recovery: Drug + Excipient 40° C./75% RH 3 weeks	Drug + Excipient 51° C. 3 weeks	Drug + Excipient + Water 40° C./75% RH 3 weeks	Drug + Excipient + Water 51° C. 3 weeks
Control (Drug alone)	—	94.67	100.53	94.60	96.64
Hypromellose 2208, USP, 3 cps	10:1	99.209	93.248	93.811	97.421
Sodium Lauryl Sulfate (SLS)	5:3	99.947	98.763	95.466	95.088
Crospovidone, NF	10:1	100.080	98.908	97.201	105.716
Polysorbate-80, NF BP/EP (vegetable source)	10:1	98.301	90.961	99.908	81.405

From the results shown in the table, the following conclusions can be drawn. Hypermellose 2208, SLS, crospovidone and polysorbate-80 are compatible with pantoprazole sodium sequihydrate at 40° C./75% RH for 3 weeks. Hypromellose 2208, SLS and crospovidone are compatible with pantoprazole sodium sequihydrate at 40° C./75% RH and 51° C. with and without additional water for 3 weeks.

In this study degradation compounds were not studied. However, the pediatric clinical formulation, [pantoprazole sodium sesquihydrate 45.24% w/w; microcrystalline cellulose 27.25% w/w; polysorbate 80 5% w/w; crospovidone 15% w/w; hypromellose 2208 1% w/w; sodium carbonate 6.5% w/w; purified water q.s.], was studied under accelerated

conditions of 40° C./75% RH and is stable up to 6 months, providing a 2 year room temperature shelf life.

The components of the pediatric formulation are provided in the following Table V.

Formulation:	Multiparticulates	
Ingredients	Amount/Capsule	% w/w
Core:		
Pantoprazole Sodium Sesquihydrate	45.11	21.911
Microcrystalline Cellulose, NF/EP (Avicel PH 101)	27.39	13.304
Polysorbate 80, NF Vegetable source	5.00	2.429
Crospovidone, NF (Polyplasdone XL)	15.00	7.286
HPMC USP/EP (Methocel) K3	1.00	0.486
Sodium Carbonate, NF	6.50	3.157
Purified Water, USP/BP/EP		q.s. to make wet mass*
Total	100.00 mg	48.573
Enteric Coat:	100.20 mg	48.67
Eudragit L30D-55	208.00 mg	30.309
	62.40 (solids)	
Talc, USP, Altalc 500V	31.20 mg	15.155
Sodium Hydroxide, NF 1 N solution	9.30 mg	0.175
	0.36 (solids)	
Triethyl Citrate, PG/NF	6.24 mg	3.031
Purified Water, USP/BP/EP	183.38 mg*	*removed during processing
Total	204.20 mg	99.186
Final Seal Coat:	1.54 mg	0.748
Hydroxypropyl Methylcellulose, USP 2910, 6 cps	1.54 mg	0.748
Purified water, USP/BP/EP	18.99 mg*	*removed during processing
Total	205.74 mg	99.934
Talc, USP, Altalc 500V	0.14 mg	0.068
Total	205.88 mg	100.002

Example 6

Evaluation of Pantoprazole Sodium Formulation in Human Adult Subjects

In this study, 40 mg pantoprazole sodium, formulated as described, clinical pediatric formulation, was administered to healthy human adults (n=24) by sprinkling in applesauce, in tablet form, or as an aqueous suspension prepared using an inactive powder blend and water (8 in each group).

In the following Table VI, column 1 provides the pharmacokinetic (PK) parameters, AUC (area under the concentration curve), AUC_T is the area under the concentration time curve, and C_{max}, maximum concentration. The second column provides the test/reference geometric mean (GM) ratio. The third column provides the confidence interval for the GM ratio. [The FDA considers a test product to be bioequivalent to a reference product if the 90% confidence interval (CI) of the geometric mean ratio of AUC and C_{max} between the test and reference fall within 80-125%]. —The confidence interval is calculated using WinNonlin software.

TABLE VI

Human PK study Results

A. Spheroids sprinkled in applesauce:

PK parameter	Test/Reference GM ratio	90% CI for ratio*
AUC	90	84-96
AUC_T	89	84-95
Cmax	62	56-70

B. Spheroids in suspension:

PK parameter	Test/Reference GM ratio	90% CI for ratio
AUC	94	88-100
AUC_T	94	88-100
Cmax	66	60-74

The lag time in the absorption of the tablet was higher compared to the sprinkle and suspension formulations. The entire drug in the tablet is released over a small time interval and therefore a higher C_{max} is obtained. With the spheroid formulations, drug from each spheroid is released over a longer time interval and therefore the C_{max} is lower than the tablet. However, the period of time following administration that pantoprazole remained in the circulation is similar for the 3 formulations.

All documents identified herein are incorporated by reference. One of skill in the art will recognize that minor modifications to the conditions and techniques described in the specific embodiments described herein can be varied without departing from the present invention. Such minor modification and variants are within the scope of the invention as defined by the following claims.

The invention claimed is:

1. Pantoprazole multiparticulates having reduced release under gastric conditions and fast release at neutral pH, wherein each of said multiparticulates comprises: a spheroid core comprising about 20% w/w to about 45% w/w of a pantoprazole salt or a hydrate thereof, as the sole active component in the multiparticulate and about 25% to about 30% w/w microcrystalline cellulose, about 4% to about 6% w/w polysorbate 80, about 14% to about 16% w/w crospovidone, about 0.5 to about 2% w/w hydroxypropyl methylcellulose, about 5% to about 8% w/w sodium carbonate, and about 1 to about 2% w/w water;

an initial seal coat comprising hydroxypropylmethyl cellulose on the spheroid core; and

an enteric coat on the initial seal coat,

wherein said multiparticulates have an average diameter of about 0.7 mm to about 1.25 mm.

2. The multiparticulates according to claim 1, wherein the pantoprazole salt is selected from pantoprazole sodium and pantoprazole magnesium.

3. The multiparticulates according to claim 1, wherein the hydrate is a sesquihydrate.

4. The multiparticulates according to claim 1, wherein the pantoprazole salt or hydrate thereof is present in an amount of about 45% w/w.

5. The multiparticulates according to claim 1, wherein said multiparticulates have an average diameter of about 1 mm.

6. The multiparticulates according to claim 1, wherein said enteric coat comprises about 48% w/w of the particulate.

7. The multiparticulates according to claim 1, further comprising a final seal coat on the enteric coat.

8. The multiparticulates according to claim 7, wherein the final seal coat comprises about 0.1 to 10 wt % of the multiparticulates.

9. The multiparticulates according to claim 7, wherein the final seal coat comprises hydroxypropyl methylcellulose (hypromellose).

10. The multiparticulates according to claim 1, wherein said initial seal coat is in the range of about 2 to about 4% w/w of the weight of the uncoated core.

11. The multiparticulates according to claim 1, wherein the enteric coating comprises about 30% w/w of methacrylic acid and methyacrylate copolymer, about 15% w/w talc, about 3% triethyl citrate and a pH adjuster; said amounts being by weight of the multiparticulates.

12. Pantoprazole multiparticulates having reduced release under gastric conditions and fast release at neutral pH, wherein each of said multiparticulates comprises: a spheroid core comprising a pantoprazole salt or a hydrate thereof in an amount of about 40% w/w free pantoprazole, as the sole active component in the multiparticulate and about 25% to about 30% w/w microcrystalline cellulose, about 4% to about 6% w/w polysorbate 80, about 14% to about 16% w/w crospovidone, about 0.5 to about 2% w/w hydroxypropyl methylcellulose, about 5% to about 8% w/w sodium carbonate, and about 1 to about 2% w/w water; an initial seal coat comprising hydroxypropylmethyl cellulose on the spheroid core; and an enteric coat on the initial seal coat, wherein said multiparticulates have an average diameter of about 0.7 mm to about 1.25 mm.

13. A product comprising a plurality of pantoprazole multiparticulates, each comprising a spheroid core comprising a pantoprazole salt or a hydrate thereof in an amount of about 40% w/w free pantoprazole, as the sole active component in the multiparticulate and about 25% to about 30% w/w microcrystalline cellulose, about 4% to about 6% w/w polysorbate 80, about 14% to about 16% w/w crospovidone, about 0.5 to about 2% w/w hydroxypropyl methylcellulose, about 5% to about 8% w/w sodium carbonate, and about 1 to about 2% w/w water; an initial seal coat comprising hydroxypropylmethyl cellulose on the spheroid core; and an enteric coat on the initial seat coat, wherein said multiparticulates have an average diameter of about 0.7 mm to about 1.25 mm.

14. The product according to claim 13, comprising about 10 mg to about 100 mg pantoprazole, based upon the weight of free pantoprazole base.

15. The product according to claim 14, comprising about 40 mg pantoprazole, based upon the weight of free pantoprazole base.

16. The product according to claim 14, wherein said plurality of multiparticulates are in an aqueous suspension.

17. The product according to claim 14, wherein said plurality of multiparticulates are in a capsule.

18. A method of producing a multiparticulate formulation of pantoprazole having reduced release under gastric conditions and fast release at neutral pH, said method comprising: producing a spheroid core comprising a pantoprazole salt or a hydrate thereof in an amount of about 40% w/w free, as the sole active component in the multiparticulate and about 25% to about 30% w/w microcrystalline cellulose, about 4% to about 6% w/w polysorbate 80, about 14% to about 16% w/w crospovidone, about 0.5 to about 2% w/w hydroxypropyl methylcellulose, about 5% to about 8% w/w sodium carbonate, and about 1 to about 2% w/w water, via extrusion and spheronization; applying an initial seal coat comprising hydroxypropyl methyl cellulose to the spheroid core; applying an enteric coating to the initial seal coated spheroid core, said enteric coating comprising a copolymer of methacrylic acid and methacrylates; and optionally applying a final seal coat to the enteric-coated spheroid core, said final seal coat being about 1 wt % of the multiparticulate; wherein the multiparticulates have an average diameter of about 0.7 mm to about 1.25 mm.

19. The method according to claim 18, wherein the spheroid core is prepared by mixing the ingredients in a low shear mixer at low shear conditions at a range of about 25 rpm to 35 rpm.

20. The method according to claim 19, wherein the low shear conditions are 32 rpm.

21. The method according to claim 18, wherein the spheroid cores are dried at a low temperature not exceeding about 40° C. for a period of 8 to 72 hours to a percent (%) loss-on-drying (LOD) of 3.4% to 4.3%.

22. The method according to claim 18, further comprising the step of applying a layer of talc in an amount of 0.05% w/w to 0.1% w/w of the multiparticulates.

23. The method according to claim 18, wherein the enteric coating is sprayed as a suspension onto the spheroid core.

24. A method of treating ulcers of the stomach and duodenum, gastroesophageal reflux disease (GERD), or Zollinger-Ellison Syndrome in a mammalian subject, comprising the step of administering to the subject a plurality of pantoprazole multiparticulates according to claim 1 comprising about 10 mg to about 100 mg pantoprazole, based upon the weight of free pantoprazole base.

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