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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 10-041-742

**TÍTULO SOLICITADO: METODOS PARA EL TRATAMIENTO DE
DESORDENES GASTROINTESTINALES
INDEPENDIENTES DE LA INGESTA DE ALIMENTO.**

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10/10/2008**

**SOLICITANTE: TAKEDA PHARMACEUTICAL NORTH AMERICA
NORTH AMERICA INC.**

APODERADO: CASTELLANOS ABONDANO MARGARITA.

TRÁMITE: REMISIÓN DE INFORMACIÓN.

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 **LABORATORIOS LEGRAND S.A.**, dentro del trámite de la referencia, por medio del presente escrito, procedo a presentar argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 18 y 20-d de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

I. REMISION DE INFORMACIÓN.

La solicitud colombiana en trámite 10-041-742 que se refiere a una composición farmacéutica que comprende (a) una primera partícula sólida, donde dicha primera partícula sólida comprende un agente activo y un primer recubrimiento entérico, donde el primer recubrimiento entérico libera el agente activo de la partícula sólida a un pH de cerca de 5.0 a cerca de 5.5., y (b) una segunda partícula sólida, donde dicha segunda partícula sólida comprende un agente activo y un segundo recubrimiento entérico, donde el segundo recubrimiento entérico libera el agente activo de la partícula sólida a un pH de cerca de 6.2 a cerca de 6.8; en donde la primera partícula sólida comprende desde cerca de 15% a cerca de 50% en peso de la composición farmacéutica y la segunda partícula sólida comprende desde cerca de 50% a cerca de 85% en peso de la composición farmacéutica; y además donde dicha composición farmacéutica se puede administrar a un paciente independiente de la ingestión de alimento.; no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, para el efecto de “recubrimiento entérico” que se reivindica para dichos gránulos recubiertos, es indispensable indicar que se reconocen dentro de la categoría de “comprimidos especiales” aquellos comprimidos que presentan algunas características farmacocinéticas diferentes a las descritas para los comprimidos convencionales, también que dentro de esta categoría, los de mayor utilización son los sublinguales, bucales, masticables, efervescentes, multicapas, vaginales, de implantación, recubiertos y de liberación controlada¹. A los últimos mencionados, corresponderían las características de la formulación que reivindica la solicitud colombiana en trámite.

Específicamente, y dentro de las posibilidades de la liberación controlada que se reconocen en el estado de la técnica, las características de la formulación contenida en las reivindicaciones de la solicitud en trámite, puede clasificarse como una formulación de liberación localizada, en donde el principio activo se libera cuando existe un pH adecuado, a través de la aplicación de un

¹ Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 142.

recubrimiento gastroresistente o entérico². Como cualquier persona medianamente versada en la materia también reconoce, este tipo de recubrimiento puede ser realizado por cualquiera de las técnicas descritas en el estado de la técnica, así como se reconoce que los materiales que se pueden usar para dicho recubrimiento son polímeros de naturaleza ácida que en función de su pK y del pH del medio, se mantienen no disociados (o poco solubles) o se disociaran (solubles), siendo el polímero ideal aquel que se disuelve o se hace permeable a un pH próximo o superior a 5³. Asimismo, se reconocen dentro de los polímeros más utilizados para conseguir el efecto descrito, el acetofalato de celulosa, el acetofalato de polivinilo, los copolímeros de ácido acrílico, la goma laca, el ftalato de hidroxipropilmetilcelulosa, entre otros.

Sin duda alguna la formulación descrita por la solicitud en cuestión, corresponde a una de aquellas que obtiene sus características de liberación sostenida mediante la inserción del fármaco en un sistema polimérico gastroresistente o entérico, que obedece a la totalidad de las características técnicas convencionales de este tipo de sistema.

En otras palabras, el tipo de recubrimiento al que se refiere la solicitud colombiana en trámite, corresponde en su totalidad a las características técnicas convencionales y ampliamente descritas en el estado de la técnica, y cualquier persona medianamente versada en la materia podría en principio involucrar este efecto de liberación localizada dependiente del pH, aplicando adecuadamente los respectivos ensayos de preformulación y formulación, más aún si se tiene en cuenta que la composición finalmente recubierta corresponde a un granulado, y que la obtención de gránulos de igual forma se encuentra ampliamente descrita⁴ en el arte.

En un segundo aspecto, en lo referente a la reivindicación 2 en donde explícitamente se menciona *“Además donde una cantidad terapéuticamente efectiva de dicha composición farmacéutica puede administrarse a un paciente independientemente de la ingesta de alimento”*, es indispensable indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 artículo 20 a cuyo tenor *“No*

² Ibid. Página 154.

³ Ibid. Página 154.

⁴ Ibid. Páginas 107 a 125.

serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales.” Dicha mención de una “*cantidad terapéuticamente efectiva*” que “*puede administrarse a un paciente independientemente de la ingesta de alimento*” tiene el mismo efecto que las reivindicaciones sobre métodos de tratamiento médico, dado que la “*cantidad terapéuticamente efectiva*” es equivalente a la dosis, en este caso, referente a la dosificación de la formulación farmacéutica, lo cual no pertenece a la categoría de producto o proceso, sino que hace referencia la forma en la que un producto se utiliza terapéuticamente, y por lo tanto no hace parte de las actividades industriales sino de las actividades médicas.

En otras palabras la dosificación o los cambios en la dosificación dentro de un producto farmacéutico no tiene naturaleza inventiva, y no cumplen con el estándar de aplicación industrial, dado que dichas modificaciones solo tienen efectos en el organismo (verificables a nivel clínico) y no efectos técnicos.

Por su parte la solicitud de patente americana US 2006/0018964 publicada el 26 de enero de 2006, revela:

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

(...)

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

(...)

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

(...)

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

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

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

(...)

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

(...)

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

(...)

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

Como se puede apreciar con toda claridad, el anterior documento revela absolutamente todas las características técnicas que definen las formulaciones farmacéuticas reivindicadas por la solicitud en trámite; es decir, composiciones farmacéuticas sólidas compuestas por partículas o gránulos recubiertos con un recubrimiento entérico, comprendiendo un principio activo tal como el lansoprazol o sus enantiómeros ópticamente puros (entre los que se encontraría Dexlansoprazol), inclusive revela copolímeros de ácido metacrílico como material de recubrimiento.

En relación con lo anterior, también se puede demostrar que específicamente los copolímeros de metacrilato tipo A y tipo B mencionados por la solicitud colombiana en trámite, ya se encuentran descritos de manera específica en el estado de la técnica, a través de documentos como por ejemplo la patente americana US 5889051 publicada el 30 de marzo de 1999, que revela:

A stable solid dispersion of prostaglandin drug, particularly Misoprostol, ($\pm$)methyl 7-[3(α)-hydroxy-2- β -(4 (RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl] heptanoate, comprising ammonio methacrylate copolymers. The ammonio methacrylate copolymers comprise Eudragit RS series, Eudragit RL series, Eudragit S, Eudragit L, and the mixture thereof. The stable solid dispersion is a sustained release type.

(...)

In accordance with the present invention, the ammonio methacrylate copolymer used in the stable solid dispersion of prostaglandin drug may be selected from the group consisting of Eudragit S (methacrylic acid copolymer, Type B, USP), Eudragit L (methacrylic acid copolymer, Type A, USP), and the mixture thereof.

En conclusión, cualquier persona medianamente versada en la formulación de productos farmacéuticos debe reconocer que el mismo principio activo se puede presentar en diferentes formas, por ejemplo, como comprimido, cápsula o solución acuosa y/o para su administración parenteral, los cuales, a su vez, se pueden formular utilizando diferentes excipientes farmacéuticamente aceptables. Reivindicar nuevas presentaciones farmacéuticas (SENFs) de fármacos ya descritos en el estado de la técnica⁵ y/o con excipientes o vehículos farmacéuticamente aceptables igualmente reconocidos, o reivindicar unas característica técnicas particulares que se asocian con ciertos efectos, como la liberación controlada por ejemplo, no pueden sustentar nivel inventivo alguno, dado que ensayar dichos principios activos junto a dichos excipientes para conseguir dichos efectos técnicos, por lo general, forma parte de la capacidad habitual de dicha persona versada en formulación de productos farmacéuticos.

En otras palabras, y teniendo en cuenta la información expuesta con anterioridad, existían al momento de presentarse la solicitud prioritaria correspondiente al expediente de la referencia los suficientes lineamientos técnicos, para que una persona medianamente versada en la formulación de productos farmacéuticos, pudiese obtener unas formulaciones farmacéuticas con idénticas características técnicas que las reivindicadas por la solicitud colombiana en trámite.

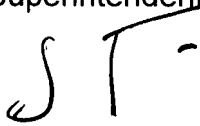
Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales, y que en consecuencia el Despacho decrete, además de la negación de la solicitud en comento, el archivo del expediente que lo contiene.

II. ANEXOS.

- Vila Jato. J.L. Tecnología Farmacéutica. Volumen II, página 107 a 125, 142, y 154.

- La solicitud de patente americana US 2006/0018964 publicada el 26 de enero de 2006.
- La patente americana US 5889051 publicada el 30 de marzo de 1999.
- La patente americana US 6462058 publicada el 8 de octubre de 2002.

Señor Superintendente,



JOSE LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

⁵ Patente americana US 6462058 publicada el 8 de octubre de 2002.

- Debido a que el proceso se realiza en seco, se produce gran cantidad de polvo y se generan cargas electrostáticas en los componentes durante las operaciones de pulverización y mezclado, las cuales pueden originar una distribución no uniforme del principio activo en el comprimido final.

Las etapas previas, utilizadas básicamente en la compresión directa, incluyen únicamente las operaciones de pulverización y mezclado. Un esquema de este método de preparación de comprimidos se recoge en la figura 2.23.

2.2.7. Comprimidos obtenidos por compresión de un granulado

La granulación tiene como objetivo la transformación de partículas de polvo cristalizado o amorfo en agregados sólidos más o menos resistentes y porosos denominados granulados. Las partículas se unen mediante enlaces interatómicos e intermoleculares de diferente naturaleza: fuerzas de Van der Waals, enlaces por puentes de hidrógeno, puentes sólidos de sustancias cristalinas, etc. El granulado constituye un estado intermedio, no sólo en la fabricación de comprimidos sino también de otras formas farmacéuticas como cápsulas rígidas, sellos y sobres, aunque puede utilizarse como tal.

Las principales razones por las que se recurre a la granulación son:

- Prevenir la segregación de los componentes en el mezclado de polvos, debidas a diferencias en el tamaño y densidad de las partículas de los componentes. Un granulado ideal (figura 2.24) contendrá todos los componentes de la mezcla en cada gránulo, evitando de esta forma la segregación de componentes.
- Mejorar las propiedades de flujo de la mezcla. Los gránulos obtenidos a partir de un sistema cohesivo son más grandes, esféricos e isodiamétricos que los componentes iniciales, mejorándose así la capacidad de flujo. Además, estas propiedades reducen las fuerzas de fricción y son menores los efectos de carga eléctrica.
- Aumentar las características de compresión de la mezcla. Ello se consigue por la homogénea distribución del aglutinante como película adhesiva en la superficie de las partículas dentro del granulado.
- Favorecer la expulsión del aire interpuesto. El aire se expulsa más fácilmente al comprimir un sólido constituido por gránulos que por un polvo fino.
- Reducir significativamente la cantidad de polvo generado en el proceso de fabricación. La liberación al medio de polvo que contenga un fármaco de gran actividad puede tener graves consecuencias sobre el personal que lo maneja.
- Reducir la higroscopicidad de la mezcla. Los componentes que son ligeramente higroscópicos en forma de polvo pueden adherirse y formar una pas-

ta. La granulación puede minimizar este inconveniente, ya que los gránulos, debido a su tamaño (menor superficie específica), adsorben menor cantidad de humedad, reteniéndola pero manteniendo una buena capacidad de fluencia.

- Mejorar la velocidad de disolución. Los aglutinantes utilizados para la granulación son sustancias hidrofílicas que, en general, facilitan la humectación del producto en el tracto gastrointestinal. En consecuencia, la velocidad de disolución del fármaco suele incrementarse.
- Incrementar la densidad del producto que se va a comprimir.

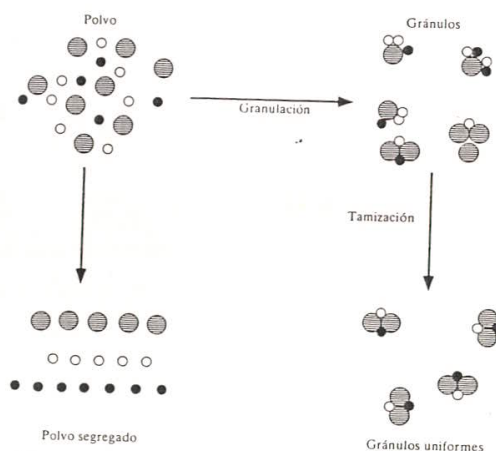


FIGURA 2.24. Esquema ilustrativo de la granulación como medio de prevenir la segregación.

Previamente a la granulación deben realizarse operaciones de pulverización y mezclado de los polvos, el cual debe efectuarse en diferentes etapas. Cuando se procede a mezclar los componentes en forma de polvos para su posterior granulación o compresión se utilizan mezcladores enérgicos, con intensa acción convectiva, como son los de cinta o de doble sigma (figura 2.25 a y b).

Una vez obtenido el granulado, deberá mezclarse con los disgregantes y lubricantes en polvo. En este caso, si se emplean mezcladores enérgicos se destruirán

muchos gránulos y se generará, inadecuadamente, una cierta cantidad de finos. En este segundo tipo de mezclado, interesa utilizar equipos sin agitadores interiores, del tipo de los mezcladores de doble cono en "V" o los rotocuboides (2.25 c y d).

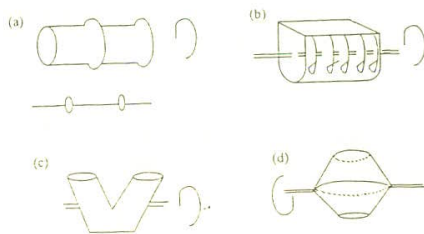


FIGURA 2.25. Esquemas de los mezcladores a) de cinta, b) doble sigma, c) doble cono y d) rotocuboide.

La preparación del granulado puede realizarse por vía seca o húmeda, que se emplee o no la adición de un disolvente. Un caso particular de esta es la pelletización, que origina conglomerados de partículas de forma más esférica y más densos que los formados en la granulación convencional.

A) Granulación por vía húmeda

La figura 2.26 recoge un esquema de las diferentes etapas que deben seguirse para obtener un comprimido por granulación húmeda. Inicialmente, se repasan los procesos ya mencionados de pulverización y posterior mezclado de los excipientes, entre los que se incluyen diluyentes, disgregantes, aglutinantes y correctores, para obtener una dispersión homogénea entre ellos. Además, la obtención del granulado por esta técnica implica la realización de las siguientes etapas:

- Humectación del polvo mezclado.
- Granulación del polvo humectado.
- Desección del granulado.
- Doble tamización.

La *humectación del polvo mezclado* tiene por objetivo conferir a las partículas, mediante la adición de un disolvente, unas características de adhesividad tales que sea posible la obtención de una masa adecuada para la granulación. La cantidad de disolvente que se adiciona constituye un factor decisivo en esta etapa. Un exceso de humedad dará lugar a la adherencia de la masa a la malla empleada para formar los gránulos y prolongará el tiempo de desecación. Por el contrario, una humedad insuficiente producirá un granulado friable, con una elevada proporción de polvo. Aunque la cantidad de humectante depende de la naturaleza de los componentes y del tamaño de gránulo deseado y, por ello, no se pueden establecer normas generales, una proporción adecuada suele estar comprendida entre 1/5 y 1/10 de la cantidad de sólido que se va a granular. En función de las propiedades de cohesión de los componentes del granulado, la humectación se realizará utilizando exclusivamente un disolvente de humectación o bien una solución del aglutinante en dicho disolvente. En cualquier caso, para garantizar una humectación homogénea de la masa, la adición debe realizarse mediante atomización. Aunque el aumento de tamaño de las partículas al aglomerarse tiene lugar fundamentalmente por acción de la película de agente aglutinante formada sobre ellas, a ello también puede contribuir otro segundo mecanismo si las partículas sólidas son solubles en el solvente de granulación. En este caso se produce una disolución parcial que da lugar a una solución saturada del sólido; posteriormente, durante el proceso de desecación, se produce una recrystalización que forma puentes sólidos entre las partículas, los cuales confieren consistencia al granulado.

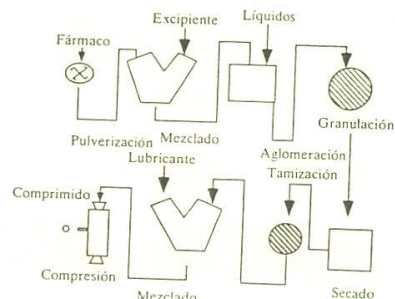


FIGURA 2.26. Etapas del proceso de compresión a partir de un granulado (granulación húmeda).

La humectación del polvo se lleva a cabo utilizando equipos de amasado, el recogido en la figura 2.27, donde se representa el esquema de un mezclador planetario utilizado en este proceso.

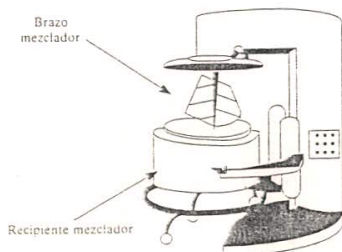


FIGURA 2.27. Esquema de un mezclador planetario empleado en el proceso de humectación.

La granulación propiamente dicha consiste en someter la masa humectada a una presión mecánica, que fuerza su paso a través de una superficie perforada (tamiz, de una determinada abertura de malla, para obtener unos pequeños granos que constituyen el granulado. El tamaño del gránulo y, en consecuencia, la abertura de malla que se debe seleccionar están condicionados por el tamaño del comprimido; se dispone de tablas que permiten la elección del tamiz más apropiado.

Es aconsejable que la malla del tamiz sea de acero inoxidable para evitar la cesión de iones metálicos que podrían alterar la formulación. Esta operación se realiza mediante distintos tipos de granuladores, los más utilizados de los cuales son los de tipo oscilante, que están constituidos por barras metálicas dotadas de un movimiento de vaivén que obliga a la masa humectada a pasar a través de un tamiz semicilíndrico (figura 2.28), dando lugar a gránulos de pequeño tamaño, porosos y de superficie relativamente lisa. Otro tipo de granuladores son los rotatorios, en los que la masa humectada es forzada a pasar a través de un tamiz ejerciendo presión mediante un rotor de paletas. El granulado obtenido suele ser más compacto y de mayor tamaño que el elaborado con los granuladores oscilantes. En general, la calidad del granulado varía de acuerdo con las características del equipo empleado: modelo, abertura de malla del tamiz, velocidad ejercida, velocidad de rotaciones u oscilaciones, etc.

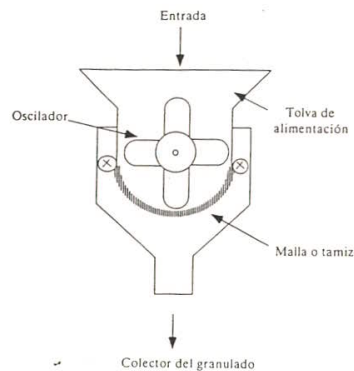


FIGURA 2.28. Esquema de un granulador oscilante.

Una vez obtenido el granulado, se procede a su desecación con objeto de eliminar el exceso de humedad. El grado de humedad considerado óptimo es del 2-3%, aunque dependerá, en cada caso, de las características particulares de los componentes incluidos en la fórmula. En este sentido, para determinar el punto final del proceso de secado, es importante conocer las humedades de equilibrio de los componentes mayoritarios del comprimido. En el caso de fármacos sensibles a la humedad y que, por tanto, requieren una desecación profunda, deberán emplearse excipientes con baja humedad de equilibrio.

En general, se recomienda que el proceso de secado, cuando se lleva a cabo por calor, se realice lenta y gradualmente, para evitar problemas de inestabilidad térmica y la formación de una costra exterior que impida la evaporación del disolvente situado en el interior del granulado. Además, en los granulados que contengan azúcares o colorantes, esta precaución evitará la caramelización y el moteado, respectivamente.

Existen diferentes sistemas para llevar a cabo la desecación del granulado. El secado en estufas o armarios de desecación se utiliza con frecuencia, aunque este procedimiento presenta algunas desventajas importantes, como son la larga duración del proceso, la migración del material disuelto hacia la superficie del lecho de partículas del granulado, debido a que el solvente se elimina sólo de la parte más superficial, y la frecuencia con la que se agregan las partículas del granulado como consecuencia de la formación de puentes sólidos entre sus puntos de contacto.

Un método alternativo para secar el granulado es la utilización de equipos de lecho fluido, los cuales son mucho más rápidos y consiguen mantener separadas las partículas del granulado durante el proceso de secado, reduciéndose los problemas de aglomeración y de migración intergranular del soluto. Otros sistemas de desecación más modernos son las radiaciones infrarrojas, la radiofrecuencia, el vacío y las microondas.

Una vez realizada la desecación del granulado, éste se somete a una *doble* para obtener la fracción granulométrica más adecuada, de acuerdo con el tamaño y peso final del comprimido. A veces se requiere una etapa previa de reducción para obtener un tamaño menor de la partícula del granulado o bien, la desagregación de los granulos adheridos. La operación se realiza con un sistema de tamices de abertura de malla igual o, más frecuentemente, con un tamiz más fino para separar el material que pueda contener el granulado. El tamaño de partícula del granulado más adecuado para la compresión está comprendido entre 350 y 700 μm , aunque es aceptable la existencia de una pequeña proporción de finos, cuyo objeto es conseguir un mejor llenado de la matriz o cámara de compresión y reducir al mínimo la pérdida de aire.

El granulado obtenido se mezcla, si se requiere, con otros excipientes como lubricantes, reguladores de flujo, disgregantes y correctores, procediendo a continuación, a su compresión.

Los métodos convencionales de granulación presentan el inconveniente de ser lentos e incluir varias etapas independientes para su realización. Por ello, se han desarrollado métodos alternativos de granulación húmeda capaces de realizar el granulado en una única etapa.

Uno de los métodos desarrollados es la *granulación por atomización* (Drier), en la que los componentes de la fórmula (diluyentes, aglutinantes, excipientes...) se suspenden en un vehículo adecuado a su naturaleza. Los sólidos constituyen de un 50 a un 60% de la suspensión y se mantienen en constante agitación para asegurar una distribución homogénea. La suspensión se bombea mediante un sistema de atomización a una cámara donde circula una corriente de aire caliente. El calor elimina el disolvente y los sólidos caen al fondo de la cámara en forma de un granulado seco y esférico, cuyo diámetro (10-250 μm) dependerá del flujo de la velocidad de atomización. La principal ventaja del proceso es la corta duración del secado y, en consecuencia, la mínima exposición del producto a la acción del calor, lo que hace el método adecuado para productos sensibles a este factor. Este sistema se obtienen granulos porosos de forma esférica que tienen muchas propiedades de flujo. Una de sus principales aplicaciones es la elaboración de los denominados "excipientes universales", útiles tras la incorporación del principio activo, y los lubricantes para la compresión directa. No obstante, si el principio activo, y los lubricantes para la compresión directa, puede obtenerse en forma estable a la temperatura y en los solventes utilizados, puede obtenerse el granulado incorporando directamente en estos excipientes el principio activo.

La *técnica del lecho fluido*, descrita por Wuster, para el mezclado, la desecación y el recubrimiento de comprimidos, tiene aplicación también en la granulación

húmeda en una sola etapa. Los componentes, incluido el principio activo, en forma de polvo fino, se suspenden en una corriente de aire dentro de un cilindro o columna cónica, produciéndose el mezclado. A continuación, se atomiza una solución adhesiva en la misma corriente de aire, de forma que el aglutinante agrega las partículas mientras se evapora el solvente. En ocasiones, el fármaco puede adicionarse junto con la solución aglutinante, aunque es más frecuente su incorporación en polvo con el resto de los componentes. Los parámetros que afectan a la calidad del granulado obtenido incluyen variables tales como la concentración y tipo de aglutinante utilizado, el líquido de granulación, la velocidad y temperatura del aire que fluidifica el lecho de partículas y la presión utilizada para atomizar el líquido de granulación. La figura 2.29 recoge un esquema de un equipo de lecho fluido para la obtención de granulos.

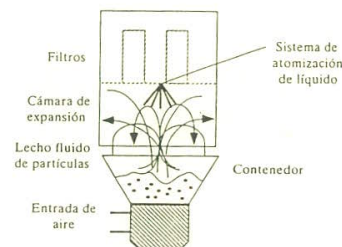


FIGURA 2.29. Granulador de lecho fluido.

Este método dinámico, a pesar de sus indudables ventajas respecto a los métodos tradicionales, especialmente en lo que se refiere al tiempo de duración del proceso y la temperatura utilizada, presenta algunas limitaciones derivadas del efecto abrasivo debido al constante roce interparticular, la aparición de cargas electrostáticas y el continuo contacto de los componentes con el aire, lo cual en algunos casos puede afectar a su estabilidad. No obstante, esta última limitación puede ser evitada utilizando algún otro tipo de gas inerte en lugar del aire.

Se han diseñado otros tipos de granuladores progresivos, como son los de paletas, los que hay numerosos modelos. Por ejemplo, los granuladores/mezcladores de alta velocidad (Diosna, Fielder), inicialmente diseñados sólo como mezcladores, están constituidos por un recipiente que contiene un eje central con tres paletas adosadas que se mueven girando en el plano horizontal y un sistema de cuchillas que giran en el plano vertical (figura 2.30).

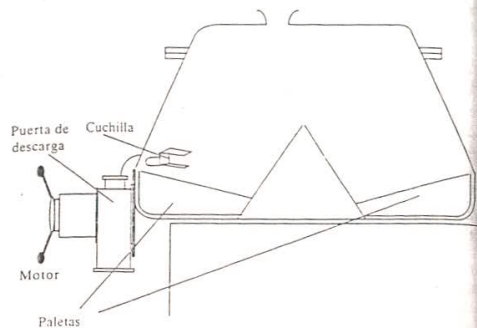


FIGURA 2.30. Esquema de un mezclador/granulador de alta velocidad.

Los componentes que van a formar parte del granulado se mezclan en un recipiente. Inicialmente, por acción del giro de las paletas y a continuación se añade el líquido de humectación, el cual se mezcla con el polvo ayudado también por este sistema de paletas giratorias. Cuando la masa está adecuadamente humectada se conecta el sistema de cuchillas cuyo objetivo es romper la pasta para producir el granulado.

La granulación por vía húmeda presenta algunas ventajas, entre las que se encuentran una mejora de las propiedades de flujo del polvo, una buena cohesión de las partículas, la prevención de la formación de polvo y la homogeneidad de la mezcla de polvos.

Sin embargo, también plantea algunos inconvenientes derivados de las operaciones largas y repetitivas que deben realizarse, el elevado consumo de energía y los altos requerimientos de mano de obra.

B) Pelletización

Para algunas aplicaciones puede ser deseable recurrir a la *pelletización*, un procedimiento estrechamente relacionado con la granulación por vía húmeda, que se define como un proceso de aglomeración que convierte los polvos finos en granulos de fármacos y excipientes voluminosos en unidades pequeñas, más fáciles de manejar y de forma más o menos esférica y de flujo libre, denominadas *pellets*.

La importancia de los *pellets* en el diseño y desarrollo de formas farmacéuticas se ha incrementado significativamente durante las últimas décadas, especialmente en el campo de las formulaciones de liberación controlada.

Los procedimientos más utilizados en la pelletización son la agitación rotatoria, la compactación, el recubrimiento y la encapsulación.

Uno de los equipos más habituales para la obtención de *pellets* es el granulador de Freund, que constituye el prototipo de los granuladores rotatorios, y en el que el polvo mezclado se añade a un recipiente donde se humecta con el solvente de granulación (figura 2.31). La base del recipiente es un disco rotatorio que gira a alta velocidad, de forma que la fuerza centrífuga obliga a mantener la masa humectada en los bordes del rotor, mientras las paredes estáticas del recipiente provocan la rotación y posterior redondeamiento de la masa para formar *pellets* de forma más o menos esférica. Posteriormente, los *pellets* se secan, en el mismo recipiente, mediante la entrada de aire caliente. Esta técnica también permite recubrirlos mediante la atomización del líquido de recubrimiento sobre los *pellets* en movimiento.

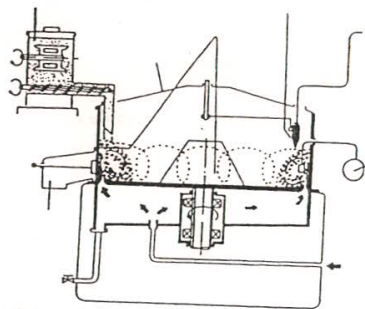


FIGURA 2.31. Esquema de un granulador de Freund utilizado para la pelletización.

Otros sistemas empleados en la pelletización incluyen la extrusión/esferonización, un esquema de cuyo proceso se recoge en la figura 2.32 y la desecación y congelación por atomización.

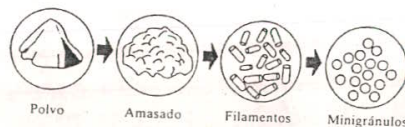


FIGURA 2.32. Diagrama esquemático de un proceso de extrusión/esferonización.

C) Granulación por vía seca

Cuando los componentes del comprimido son sensibles a la humedad, por las altas temperaturas utilizadas durante el secado o son excesivamente solubles en los medios de humectación utilizados, y si, además, poseen suficientes propiedades cohesivas, se recurre a la vía seca para formar el granulado. Este método, conocido también con el nombre de "granulación por doble compresión", no es más que un proceso que comprende dos etapas: la compresión y el triturado-tamizado. Un esquema de este procedimiento se recoge en la figura 2.33.

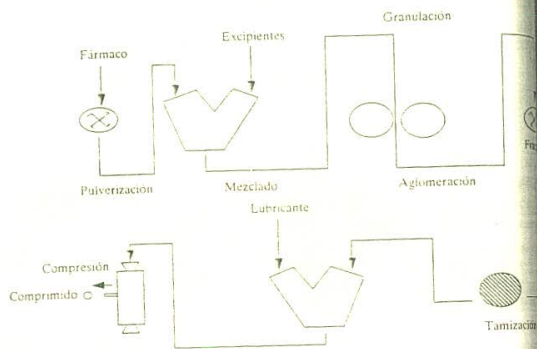


FIGURA 2.33. Etapas del proceso de compresión a partir de un granulado (granulación seca).

Las dos técnicas más importantes para realizar este tipo de granulación son el briqueteado, o *slugging*, y la compactación por rodillos. En el briqueteado se comprime directamente el polvo constituido por la mezcla del componente activo, diluyente (si lo requiere) y parte del lubricante, de los cuales al menos uno debe tener propiedades cohesivas. Si no es así, puede adicionarse un aglutinante seco, del tipo de la polivinilpirrolidona. La obtención de las briquetas se realiza mediante máquinas de comprimir excéntricas, que permiten alcanzar presiones elevadas (20-25 Tm/cm²), equipadas con un juego de matrices de gran diámetro (2,5-2,5 cm) y zonas planas. El material en polvo contiene una gran cantidad de aire, en

el proceso de compresión. Cuanto más tiempo se deja que este aire escape, mejores serán las características de la briqueta, o *slug*. Posteriormente, las briquetas se fracturan en un molino de conminución para obtener el granulado, el cual debe someterse a una doble tamización para conseguir una uniformidad de tamaño.

El rendimiento de la operación se incrementa cuando se usa el método de compactación. En esta técnica, el polvo que se ha de densificar es forzado, mediante un tornillo sin fin, a pasar entre unos rodillos de acero que giran en sentido inverso sometiendo al producto a gran presión, lo que promueve la compactación y facilita la eliminación del aire interpuesto. De esta forma se obtiene una placa comprimida de gran dureza que se fractura posteriormente, mediante un molino triturador que dará lugar a un granulado uniforme de pequeño tamaño. Entre los molinos compactadores disponibles, destaca por su utilidad y rendimiento el Chilsonator, un esquema del cual se recoge en la figura 2.34.

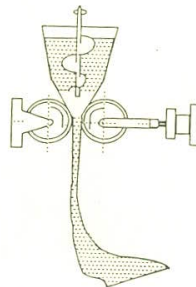


FIGURA 2.34. Esquema de un compactador Chilsonator.

A pesar de las ventajas derivadas de la simplicidad del proceso, que evita la humectación y la posterior desecación, en la granulación por vía seca se produce una gran cantidad de polvo y finos que deben ser reciclados. Por otra parte, a veces, las presiones excesivas requeridas para conseguir la cohesión de ciertos materiales prolongan el tiempo de disolución.

Mecanismos de unión entre partículas para formar gránulos o pellets

Durante los procesos de granulación o pelletización deben formarse uniones entre las partículas del polvo lo suficientemente fuertes como para evitar su rup-

tura y mantener, durante las siguientes operaciones y manipulaciones a la que se someterá, la integridad del granulado o los *pellets* formados. A continuación se describen los mecanismos más importantes responsables de la unión entre partículas del polvo.

- **Fuerzas de adhesión y cohesión por acción de películas líquidas móviles.** La humedad presente en el polvo forma una fina capa inmóvil que reduce la distancia entre las partículas y aumenta el área de contacto entre ellas. En consecuencia, las fuerzas de unión interparticulares, tales como las de Van der Waals, que son proporcionales al diámetro de las partículas, inversamente proporcionales al cuadrado de la distancia de separación, serán incrementadas. Este tipo de fuerzas tiene especial importancia en los granulados obtenidos por vía seca, ya que, al someter la masa a presión, incrementa el contacto entre las capas de adsorción, con lo que disminuye la distancia interparticular y aumenta su contribución a la cohesión del granulado.
- **Fuerzas interfaciales y presión capilar por acción de películas líquidas móviles.** Durante la granulación y pelletización por vía húmeda se añade a la mezcla de polvos un líquido que forma también películas móviles entre las partículas. La figura 2.35 muestra las diferentes formas de distribución del agua entre las partículas, propuestas por Conway-Jones.

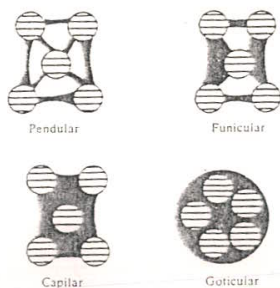


FIGURA 2.35. Distribución de las películas móviles de agua entre las partículas.

Estos puntos de unión húmedos son estructuras temporales en el granulado húmedo, ya que éste será posteriormente secado. Sin embargo,

tituyen la base de los puentes sólidos formados por los aglutinantes presentes o por los materiales que se disuelven en el líquido de granulación.

- **Puentes sólidos.** Pueden formarse por fusión parcial de algún componente endurecimiento o consolidación de los aglutinantes o bien por la cristalización de sustancias disueltas en el líquido de granulación. El segundo mecanismo es el más frecuente cuando se incluye un aglutinante en el solvente de humectación, ya que al proceder al secado, y una vez formados los puentes líquidos mencionados anteriormente, el aglutinante se endurece o cristaliza formando puentes sólidos que unen las partículas. Por otra parte, el solvente usado para granular puede disolver parcialmente algunos componentes de la formulación, que, cuando se procede al secado, da lugar a su cristalización, contribuyendo también a la unión entre partículas. Un ejemplo ilustrativo de esta situación es la adición de sacarosa en seco y la posterior humectación de la mezcla con agua.

El tamaño de los cristales que forman los puentes sólidos está influenciado por la velocidad de secado del granulado. En este sentido, es importante procurar que el principio activo no se disuelva en el líquido de granulación y luego recristalice, pues, si el tamaño de los cristales formados es mayor que el que presentaba el fármaco en su incorporación inicial a la formulación, se puede modificar su velocidad de disolución.

- **Fuerzas atractivas entre partículas sólidas.** Existen dos tipos de fuerzas atractivas entre partículas que pueden actuar en ausencia de puentes líquidos y sólidos formados por los aglutinantes: las fuerzas electrostáticas, las cuales contribuyen de forma importante en la integridad del granulado final, y las fuerzas de Van der Waals, que son aproximadamente cuatro veces más fuertes que las primeras y responsables de la cohesión en los granulados obtenidos por vía seca. La magnitud de estas fuerzas se incrementa cuando la distancia entre superficies adyacentes disminuye, lo cual se consigue mediante la compactación o presión aplicada en este tipo de granulación.

E) Mecanismos de formación de granulados y pellets

La formación y crecimiento de gránulos y *pellets* puede ocurrir de diferentes formas, dependiendo del tipo de equipo utilizado y el procedimiento seleccionado. Los principales mecanismos propuestos para su formación son la nucleación, la coalescencia, el recubrimiento y la transferencia por abrasión.

La **nucleación** se produce como consecuencia del contacto o adhesión entre partículas, debido a la formación de puentes líquidos, lo cual lleva a formar un núcleo aire-líquido-sólido.

La **coalescencia** es un mecanismo de crecimiento de los núcleos para formar partículas de mayor tamaño, consecuencia de la colisión aleatoria de los mismos. Para ello, se precisa un ligero exceso de humedad superficial.

El *recubrimiento* se consigue mediante la adición sucesiva de material húmedo sobre los núcleos ya formados. En general, la velocidad de crecimiento es lenta.

El aumento del tamaño del granulado o de los *pellets* mediante *transferencia por abrasión* consiste en el intercambio de material de unas partículas a otras sin ninguna preferencia. La figura 2.36 representa, de forma esquemática, los diferentes mecanismos de formación y crecimiento de partículas de granulado.

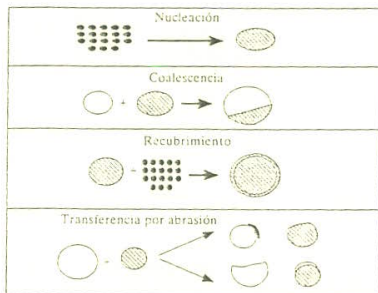


FIGURA 2.36. Mecanismos de formación y crecimiento del granulado y los pellets.

F) Control de granulados y pellets

El granulado y los *pellets*, como caso particular de aquel, deben ser sometidos a una serie de ensayos cuya finalidad es comprobar que reúnen las características adecuadas para su posterior compresión. Entre las propiedades que deben controlarse, además de la uniformidad en el contenido en principio activo, cabe citar la forma y el tamaño, la densidad, la porosidad, la dureza y friabilidad, la capacidad de flujo, el contenido en humedad y la capacidad de compresión.

El *tamaño* de las partículas del granulado y su distribución pueden determinarse por diferentes métodos, el más utilizado de los cuales es la tamización con equipos de tamices vibratorios o en los que el granulado es impulsado por la fuerza del aire. Debe prestarse atención a las condiciones de la tamización, ya que pueden requerirse condiciones especiales para algunos productos debido a su fragilidad, electricidad estática, etc.

El *tamaño* de las partículas del granulado debe ser homogéneo, de manera que su dispersión sea la más pequeña posible y esté comprendida en unos márgenes relativamente estrechos. La proporción de finos, que generalmente están

tuidos por partículas de tamaño inferior a 100 μm , tiene gran importancia debido a su influencia negativa sobre las propiedades de flujo, aunque en los granulados para compresión interesa que exista una cierta proporción de finos para asegurar un llenado más homogéneo de la matriz. En cualquier caso, el tamaño de las partículas suele presentar una distribución logarítmico-normal, aunque pueden aplicarse otros tipos de funciones de distribución.

La *forma* es otra característica esencial de las partículas del granulado, en especial cuando van a destinarse a la compresión, debido a su influencia sobre diferentes propiedades del granulado, particularmente su capacidad de flujo. Interesa que las partículas tengan una forma regular y homogénea, habitualmente redondeada o alargada, que pueden comprobarse a simple vista o bien mediante equipos ópticos adecuados.

La *densidad aparente* de un granulado se define como la relación existente entre una cantidad determinada del mismo y el volumen aparente que ocupa dicha cantidad. El volumen del granulado viene determinado, fundamentalmente, por el tamaño, forma y textura de las partículas, las películas que las rodean (gases) y la presencia de cargas electrostáticas. Con el tiempo, y debido a las vibraciones a que se ve sometido durante su procesamiento y transporte, el volumen puede modificarse significativamente; por ello, debe realizarse una prueba que determine la relación entre los volúmenes del granulado aireado y vibrado, con objeto de prevenir modificaciones importantes en el volumen, lo que reviste especial importancia en el momento de seleccionar la capacidad de la matriz que debe ser llenada para la compresión.

La figura 2.37 muestra un dispositivo mecánico, denominado *volumenómetro de asentamiento*, que se utiliza para medir el cambio de volumen que experimenta el granulado cuando disminuyen los espacios vacíos y se produce su asentamiento. Para ello, se somete el granulado contenido en la probeta graduada a una vibración mecánica por medio de un motor que rota a velocidad constante, hasta conseguir que el volumen se mantenga sin cambios. La densidad del granulado se incrementa desde un valor inicial (D_0 : densidad del granulado vertido o aireado) hasta un valor final (D_f : densidad del granulado vibrado o consolidado).

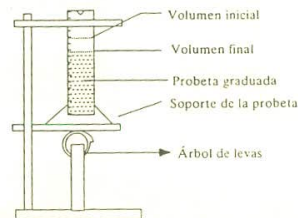


FIGURA 2.37. Esquema de un volumenómetro de asentamiento.

La relación D_f/D_o , conocida como índice de Hausner, está relacionada con la fricción interparticular y, como tal, puede utilizarse para predecir las propiedades de flujo del granulado, habiéndose demostrado que cuando la fricción interparticular es baja, como por ejemplo en los granulados esféricos de tamaño medio, la relación es próxima a 1.2, mientras que cuando los gránulos son de menor tamaño, más cohesivos y, por tanto, con menor flujo, el índice de Hausner presenta valores mayores de 1.6. Otro índice que expresa la capacidad de asentamiento es el propuesto por Carr (I_c), estrechamente relacionado también con la capacidad de flujo del granulado, y definido mediante la siguiente relación:

$$I_c = \frac{D_f - D_o}{D_o} \times 100$$

La porosidad es un parámetro estructural de gran importancia, ya que condiciona la velocidad y magnitud de la dispersión de los gránulos en un medio acuoso y, por tanto, influye en la velocidad de disolución. Además, condiciona otras propiedades relacionadas con la fragmentación y la integridad del granulado. La porosidad se define como la proporción de volumen ocupado por espacios vacíos del granulado y se expresa en porcentaje:

$$\text{Porosidad} = \frac{\text{Volumen de los poros}}{\text{Volumen aparente}} \times 100$$

Puede determinarse con un porosímetro de mercurio, en cuyo caso debe considerarse que la presión ejercida y las dimensiones de los poros condicionan la mayor o menor penetración del mercurio en los mismos. También puede recurrirse a la adsorción de un gas neutro (nitrógeno, argón, etc.), determinándose la cantidad de gas necesaria para formar una capa monomolecular uniforme sobre las partículas.

Respecto a la resistencia a la rotura del granulado, es necesario que las partículas del mismo sean suficientemente resistentes para mantener su integridad durante el transporte que va a experimentar hasta su transformación en comprimido.

Se pueden hacer medidas directas de resistencia a la fractura mediante pruebas de compresión, impacto, abrasión, atricción e incluso disolución. La velocidad y el método de aplicación de la fuerza deben estar estrechamente controlados; obstante, a menos que las partículas del granulado presenten una forma similar, un estrecho margen de tamaño, se obtendrá una gran dispersión en los valores de resistencia a la fractura.

La friabilidad del granulado puede determinarse por agitación de una muestra del mismo durante un tiempo determinado, en un envase cerrado, seguido de un nuevo control de su granulometría por tamización. Este test proporciona una

tante información sobre el tipo de mezclador que podrá ser utilizado posteriormente para la adición de los lubricantes u otros componentes, en la etapa previa a la compresión.

El ángulo de reposo (γ) constituye, junto con la densidad, una de las medidas más habituales para conocer la capacidad de flujo del granulado y se determina midiendo el ángulo de la pendiente formada por la generatriz del cono que se produce cuando se vierte libremente el granulado. La figura 2.38 presenta algunas de las formas más comunes de caracterizar este parámetro.

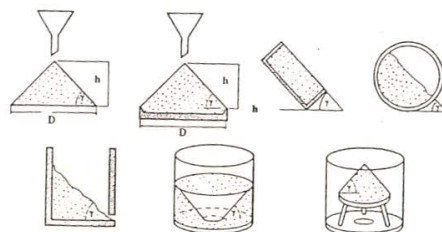


FIGURA 2.38. Formas de determinar el ángulo de reposo.

Cuanto más aplanado sea el cono, es decir, cuanto menor sea el ángulo que forma su generatriz con la horizontal, tanto mejores serán las propiedades fluyentes del granulado. El ángulo de vertido se obtiene a partir de la siguiente expresión:

$$\text{tg } \gamma = h/r$$

[2.5]

donde h es la altura del cono formado por el granulado (valor medio de varias medidas), y r , el radio de la base del cono. El flujo libre del granulado no sólo depende de la fuerza gravitacional a que está sometido, sino que también influyen sobre él las fuerzas derivadas de la fricción interparticular, por lo que existe una estrecha relación entre ángulo de reposo, flujo y forma de la partícula. En general, se establece que los granulados con un ángulo de vertido menor de 30° fluyen fácilmente; si el ángulo de vertido está comprendido entre 30° y 50° el flujo es difícil, y si el ángulo es mayor de 50° no hay flujo libre. La figura 2.39 representa la relación entre el índice de Carr, definido previamente en función de las densidades del granulado vertido y vibrado, y el ángulo de reposo, los cuales reflejan la capacidad de flujo de un lecho de partículas.

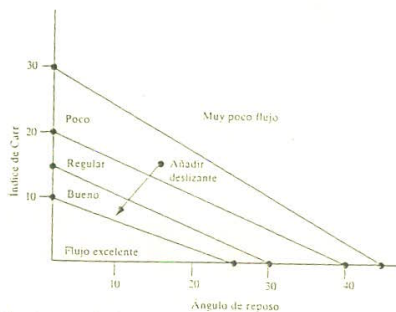


FIGURA 2.39. Relación entre el índice de Carr y el ángulo de reposo para diferentes comportamientos reológicos de los lechos de partículas.

En cuanto al *contenido en humedad*, la humedad residual del granulado es de gran importancia, fundamentalmente por su influencia sobre las características de flujo, compresión y consolidación del granulado. Además, también puede afectar significativamente la estabilidad química de algunos fármacos. La pérdida del agua por sequedad se determina mediante métodos gravimétricos; la forma más sencilla y frecuente es la utilización de una balanza de plato que lleva incorporada un termómetro de rayos infrarrojos para proceder al secado de la muestra. Si se requieren datos más exactos, se puede recurrir a la técnica de Karl-Fisher.

La determinación de la *capacidad de compresión* tiene como objeto conocer si el granulado obtenido es apto para ser comprimido. Una vez sometido a ciertas fuerzas de compresión, el granulado puede experimentar deformación elástica (recupera el volumen inicial cuando cesa la presión que lo deforma) plástica (se deforma cuando cesa la presión que lo comprime). Si bien es cierto que un material que va a comprimirse debe ser fundamentalmente plástico, es decir, con capacidad de deformación permanente, también puede presentar un cierto grado de fragmentabilidad y no debe tener capacidad para adherirse a los punzones empleados para someter el granulado a la fuerza de compresión (esto se evita mediante la adición de lubricantes).

Las propiedades de compresión del granulado, es decir, la elasticidad, plasticidad, fragmentabilidad y capacidad para adherirse a los punzones, se determinan mediante la formación de comprimidos, utilizando diferentes tiempos de aplicación de fuerza y de mezclado con el lubricante. La interpretación de los resultados obtenidos, midiendo la dureza o resistencia a la fractura de los diferentes comprimidos obtenidos, permite establecer las características de compresión del granulado.

2.2.8. Compresión

Una vez obtenido el granulado y comprobado, mediante los controles citados, que éste responde a las características deseadas, se procede a realizar, por medio de máquinas de comprimir, el proceso de compresión propiamente dicho.

A) Máquinas de comprimir

Una máquina de comprimir consta de una serie de elementos fundamentales: punzones, matriz y sistema de distribución del polvo o granulado.

Los *punzones* son los elementos mediante los cuales se va a aplicar la fuerza axial sobre el granulado. Son piezas metálicas, en general de acero inoxidable y habitualmente de forma cilíndrica. Su superficie puede ser plana o, en mayor o menor grado, cóncava, lo que da lugar a diferentes formas de comprimidos (figura 2.40). Los punzones pueden tener impresiones en sus caras para producir comprimidos que lleven marcadas ranuras o un determinado logotipo.

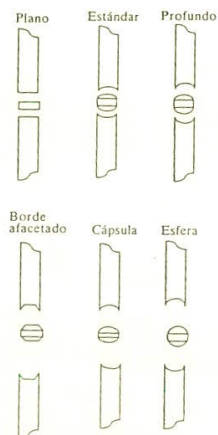


FIGURA 2.40. Punzones con caras de diferentes formas y comprimidos resultantes.

blecen que al menos un 75% del fármaco debe disolverse en 45 minutos. Con objeto de reducir la variabilidad interlaboratorio en los test de disolución, la USP sugiere el uso de discos estándares de ácido salicílico y prednisona como calibradores del equipo de disolución.

2.2.11. *Comprimidos especiales*

Se incluye dentro de esta categoría a aquellos comprimidos que presentan alguna característica farmacotécnica diferente de las descritas para los comprimidos convencionales. Los comprimidos especiales de mayor utilización (sublinguales y bucales, masticables, efervescentes, multicapa, vaginales, de implantación, de liberación sostenida y recubiertos) se describen a continuación.

A) *Comprimidos sublinguales y bucales*

Son comprimidos destinados a situarse bajo la lengua (sublinguales) o a mantenerse en la cavidad oral (bucales), donde se disuelven lentamente liberando el principio activo para producir un efecto local o ser absorbidos a través de la mucosa y ejercer un efecto sistémico. En general, presentan pequeño tamaño y una forma plana u oval. Los comprimidos bucales deben disolverse con lentitud, para lo cual en su formulación se evita la presencia de agentes disgregantes y se incorporan aglutinantes enérgicos (gelatina, goma arábiga, carboximetilcelulosa...) y lubricantes de acción hidrofóbica, del tipo del estearato magnésico, que contribuyen a aumentar el tiempo de disgregación. Además, se utilizan fuerzas elevadas de compresión para obtener comprimidos duros. Se pueden administrar de esta forma hormonas como la metiltestosterona, el citrato de oxitocina, la progesterona, antisépticos y antibióticos, etc.

Los comprimidos sublinguales suelen contener fármacos que serían destruidos o inactivados a su paso por el tracto gastrointestinal. En general, están concebidos para que el principio activo se ceda lentamente, de manera que la velocidad de liberación sea del mismo orden de magnitud que la de absorción para asegurar el máximo aprovechamiento de la dosis administrada. Si la liberación se produjera muy rápidamente, la mucosa no estaría en situación de absorber toda la cantidad de fármaco disuelta, por lo que una parte de éste sería deglutida junto con la saliva. Por el contrario, en ciertos casos especiales, cuando se recurre a esta forma de administración para el tratamiento de situaciones urgentes, como la angina de pecho o el asma, los comprimidos sublinguales deben disolverse fácilmente, permitiendo una rápida absorción del fármaco, por lo que para su obtención se emplean bajas fuerzas de compresión y se les dota de una forma lenticular y de gran superficie. De este modo se administran fármacos tales como la nitroglicerina, el clorhidrato de isoproterenol, el sulfato de isoprenalina, el dinitrato de isosórbida, la ketanserina, etc.

D) Recubrimiento gastrorresistente

El recubrimiento gastrorresistente o entérico, que puede ser realizado por cualquiera de las técnicas de recubrimiento descritas anteriormente, está especialmente indicado en aquellos casos en que se requiere:

- Proteger fármacos inestables en medio ácido de la acción de los fluidos gástricos (por ejemplo las enzimas y ciertos antibióticos).
- Proteger el estómago del efecto irritante de ciertos fármacos (por ejemplo el naproxeno, el diclofenac).
- Liberar preferentemente los fármacos en el intestino para conseguir una acción local (por ejemplo los antihelmínticos y los antisépticos).
- Facilitar la absorción de fármacos absorbidos preferentemente en el intestino delgado.

Los materiales de recubrimiento entérico deben garantizar la integridad de la cubierta a su paso por el estómago, manteniéndose impermeables e insolubles al pH gástrico, que oscila entre 1,5 y 4, y durante el tiempo de tránsito, que varía considerablemente de unas situaciones a otras, en especial con la presencia de alimentos (0,5-5 h, con un tiempo medio de aproximadamente 3 h).

Como materiales de recubrimiento se emplean, habitualmente, polímeros de naturaleza ácida que, en función de su pK y del pH del medio, se mantendrán no disociados (poco solubles) o se disociarán (solubles). El polímero ideal es aquel que se disuelve o se hace permeable a un pH próximo o superior a 5. Entre los más utilizados se pueden citar el acetofalato de celulosa, el acetofalato de polivinilo, los copolímeros del ácido metacrílico (Eudragits®), la goma laca, el ftalato de hidroxipropilmetilcelulosa, etc. Para conseguir un perfil de liberación adecuado se suele recurrir a la mezcla de diferentes agentes filmógenos. La figura 2.61 recoge el perfil de disolución, en función del pH, de los Eudragits L y S y de mezclas de los mismos en distintas proporciones.

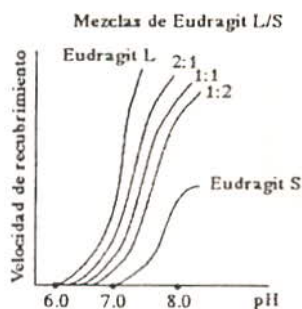


FIGURA 2.61. Perfil de disolución de diferentes mezclas de Eudragits L y S, en función del pH.



US005889051A

United States Patent [19]
Chen et al.

[11] Patent Number: 5,889,051
[45] Date of Patent: Mar. 30, 1999

- [54] STABILIZATION OF PROSTAGLANDIN
DRUG
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- [21] Appl. No.: 893,265
- [22] Filed: Jul. 15, 1997
- [51] Int. Cl.⁶ A61K 31/215
- [52] U.S. Cl. 514/530; 514/964
- [58] Field of Search 514/530, 964

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Primary Examiner—Leonard Schenkman
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.

[57] ABSTRACT

A stable solid dispersion of prostaglandin drug, particularly
Misoprostol, (±)methyl 7-[3(α)-hydroxy-2-β-(4 (RS)-4-
hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl]
heptanoate, comprising ammonio methacrylate copolymers.
The ammonio methacrylate copolymers comprise Eudragit
RS series, Eudragit RL series, Eudragit S, Eudragit L, and
the mixture thereof. The stable solid dispersion is a sustained
release type.

24 Claims, 3 Drawing Sheets

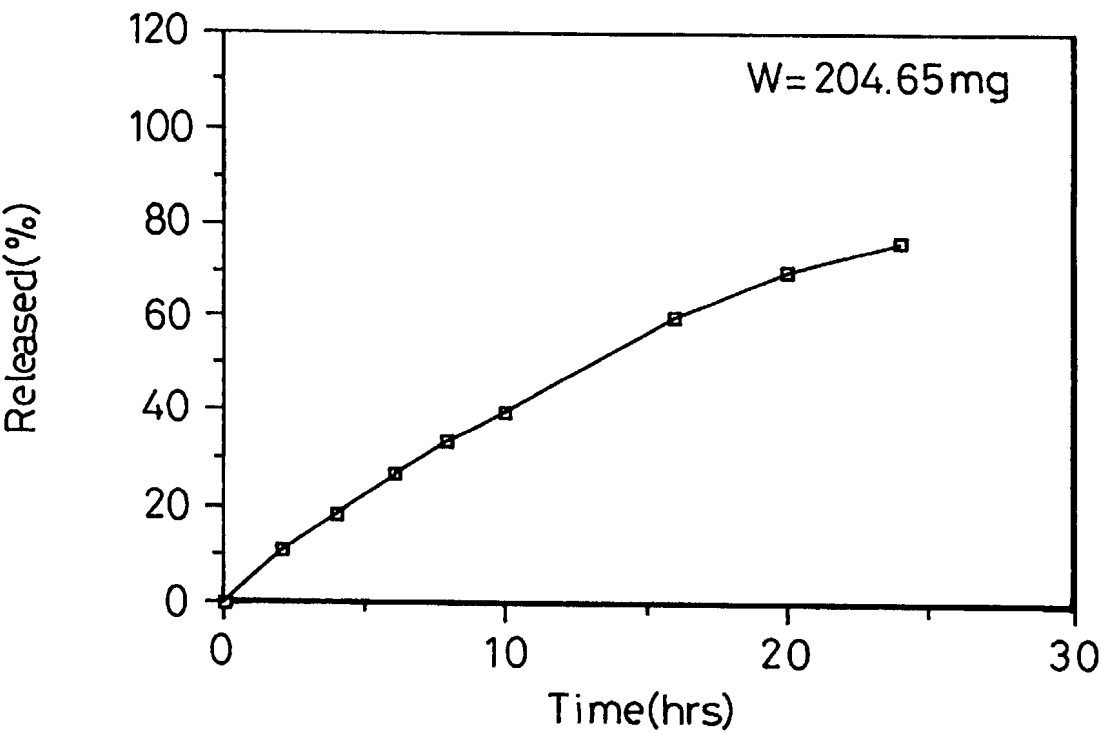


FIG. 1

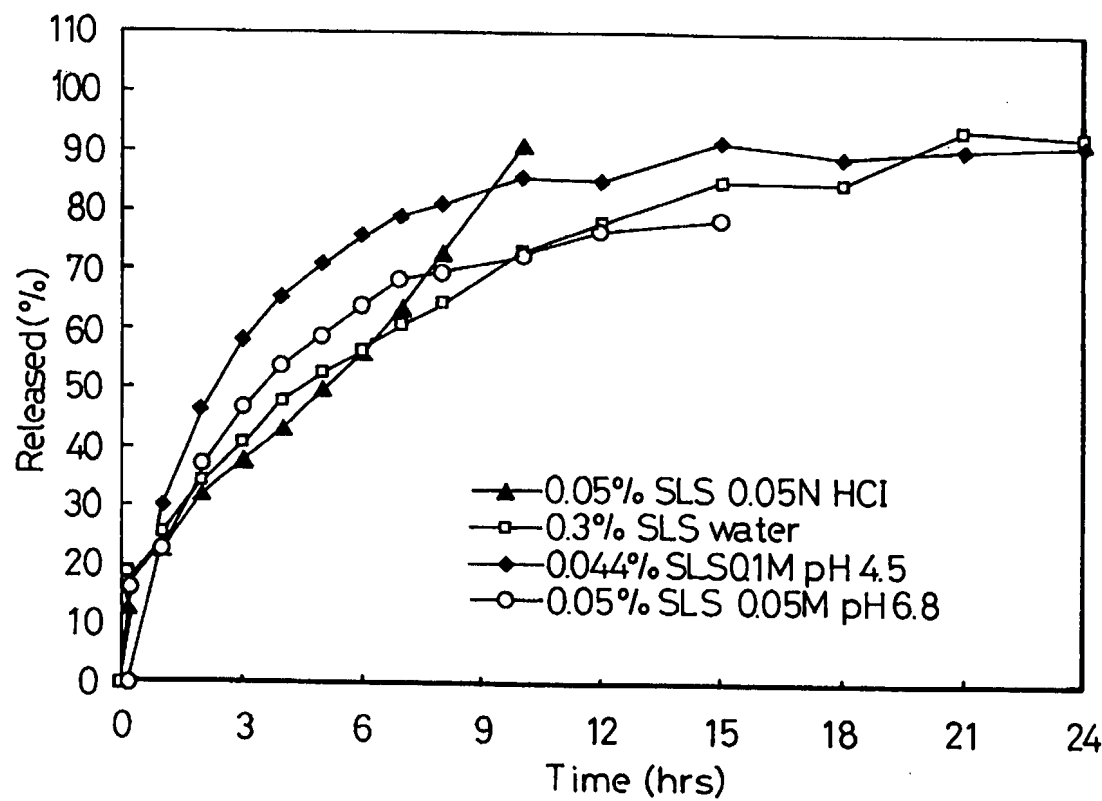


FIG. 2

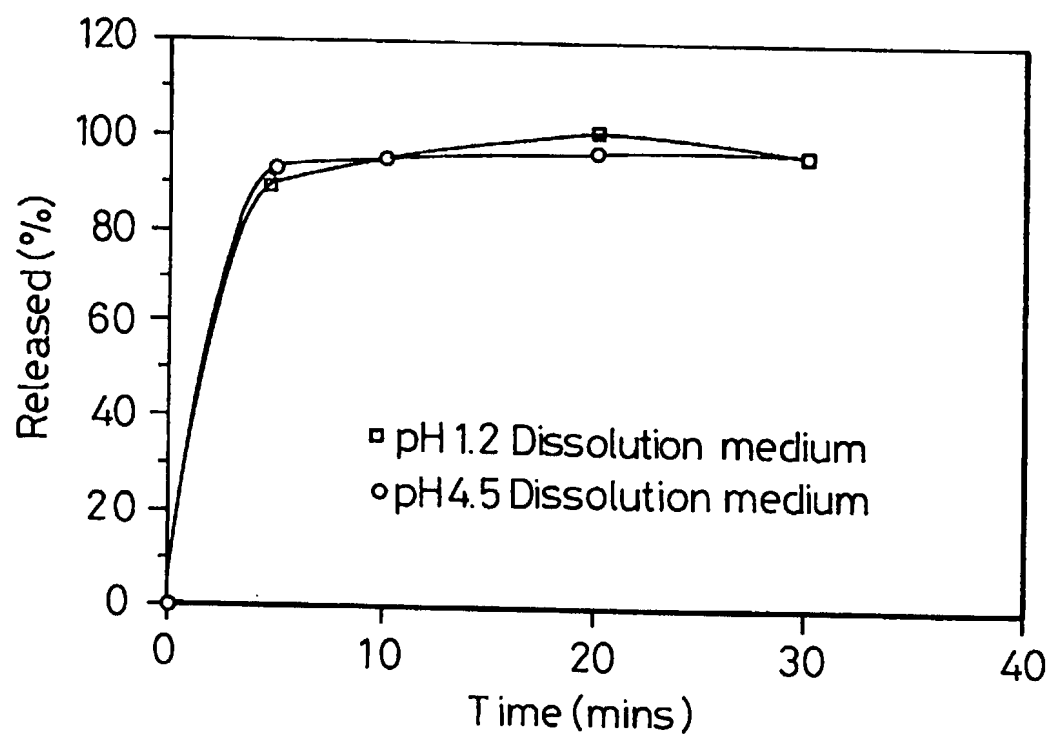


FIG. 3

STABILIZATION OF PROSTAGLANDIN DRUG

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a stable solid dispersion of a prostaglandin drug, in particular, to a stable solid dosage of Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate, by using ammonio methacrylate copolymers.

2. Description of the Prior Art

U.S. Pat. No. 3,965,143 discloses ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate, a potent antiseecretory agent. The above compound, also known as Misoprostol, is a prostaglandin E-type drug.

Misoprostol is difficult to formulate due to its instability. The present invention provides stabilized compositions of the above anti-secretory agent. Particularly, the present invention provides a stable solid dispersion of Misoprostol for use in sustained release and a method of producing the same.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a stable solid dispersion of a prostaglandin drug comprising an ammonio methacrylate copolymer which is useful for stabilization.

Another object of the present invention is to provide a stable solid dispersion of Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate, comprising an ammonio methacrylate copolymer which mitigates the above drawbacks.

A further object of the present invention is to provide a stable solid dispersion of Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate, which is sustained release and can be used as a long term dosage.

It is still another object of the present invention to provide a method of preparing a stable solid dispersion of prostaglandin drug, particularly Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate, by using a solvent stripping technology.

These and other objects, advantages and features of the present invention will be more fully understood and appreciated by reference to the written specification and appended drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be further explained with reference to the annexed drawings, wherein:

FIG. 1 is a dissolution profile of the sustained release solid dispersion of Misoprostol of Example 7;

FIG. 2 is a dissolution profile of the sustained release Misoprostol tablets of Example 10; and

FIG. 3 is a dissolution profile of a commercial available Misoprostol immediate release tablet.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a stable solid dispersion of a prostaglandin drug comprising from about 1 to about 1000

parts of an ammonio methacrylate copolymer, based on 1 part of prostaglandin drug. Preferably, the stable solid dispersion of prostaglandin drug of the present invention comprises from about 10 to about 450 parts of the ammonio methacrylate copolymer, based on 1 part of prostaglandin drug. The stable solid dispersion is a sustained release type.

The prostaglandin drug is such as, Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1-yl]heptanoate. Misoprostol, as known in the art, has the molecular weight of 382.5 and four isomers. U.S. Pat. No. 3,965,143 directed to the Misoprostol is incorporated herein for reference in its entirety. Furthermore, the present invention is capable of stabilizing any pharmaceutically active compounds, particularly those of which the properties are similar to that of Misoprostol.

According to the present invention, the ammonio methacrylate copolymer is selected from the group consisting of Eudragit RS (ammonio methacrylate copolymer, Type B, USP) series, Eudragit RL (ammonio methacrylate copolymer, Type A, USP) series, and the mixture thereof. It should be understood that the ammonio methacrylate copolymer used in the present invention is not limited to the Eudragit RS series and the Eudragit RL series.

Eudragit RS is a tripolymer of ethyl acrylate, methyl methacrylate, and trimethylammonioethyl methacrylate chloride of which the molar proportion of the monomer units is at a ratio of 1:2:0.1 and has a mean molecular weight about 150,000. Furthermore, the Eudragit RS could have any molar ratio of an ammonium group to the remaining neutral (meth)acrylic acid ester group. Preferably, the Eudragit RS has a molar ratio of an ammonium group to a (meth)acrylic acid ester group of 1:40. The Eudragit RS in the present invention is selected from the group consisting of Eudragit RSPM, Eudragit RSPO, Eudragit RS100, Eudragit RS12.5, and the mixture thereof. The wording "Eudragit RSPM" represents general ungrounded powders of Eudragit RS, the wording "Eudragit RSPO" represents grounded fine powders of Eudragit RS, and the wording "Eudragit RS100" represents granules of Eudragit RS, while the wording "Eudragit RS12.5" represents Eudragit RS solution products of which Eudragit RS is dissolved in an organic solvent.

Similarly, Eudragit RL is a tripolymer of ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride of which the molar proportion of the monomer units is at a ratio of 1:2:0.2 and has a mean molecular weight about 150,000. The Eudragit RL could also have any molar ratio of an ammonium group to the remaining neutral (meth)acrylic acid ester group. Preferably, the Eudragit RL has a molar ratio of an ammonium group to a (meth)acrylic acid ester group of 1:20. Furthermore, the Eudragit RL in the present invention is selected from the group consisting of Eudragit RLPM, Eudragit RLPO, Eudragit RL100, Eudragit RL12.5, and the mixture thereof. The wordings "PM," "PO," "100," and "12.5" are defined as above. The mixture of the Eudragit RS series and the Eudragit RL series at any ratio is also used as the ammonio methacrylate copolymer of the present invention.

In accordance with the present invention, the ammonio methacrylate copolymer used in the stable solid dispersion of prostaglandin drug may be selected from the group consisting of Eudragit S (methacrylic acid copolymer, Type B, USP), Eudragit L (methacrylic acid copolymer, Type A, USP), and the mixture thereof.

Eudragit S is a copolymer of methacrylic acid and methyl methacrylate of which the molar proportion of the monomer

units is at a ratio of 1:2 and has a mean molecular weight about 135,000. Eudragit L is a copolymer of methacrylic acid and methyl methacrylate of which the molar proportion of the monomer units is at a ratio of 1:1 and also has a mean molecular weight about 135,000. The mixture of the Eudragit S and the Eudragit R at any ratio is also used as the ammonio methacrylate copolymer of the present invention.

The present invention also provides a method of preparing a stable solid dispersion of prostaglandin drug comprising the following steps:

- (1) dissolving a prostaglandin drug in a solvent to form a solution;
- (2) adding an ammonio methacrylate copolymer into the solution to form a mixture and stirring the mixture for a period of time;
- (3) flash evaporating the solvent and blow-drying a residue after evaporation to obtain a solid dispersion;
- (4) drying the solid dispersion; and
- (5) grinding and sieving the solid dispersion to obtain a resultant product.

The prostaglandin drug is such as, Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate. Further, the method of the present invention is capable of stabilizing any pharmaceutically active compounds, particularly those of which the properties are similar to that of Misoprostol.

The solvent used in step (1) can be those known in the art and used in any suitable amount. The solvent suitable for use in the preparation of the solid dispersion of the present invention includes ethanol, such as ethanol 200 proof grade, ethanol 3A grade, ethanol USP, ethanol absolute GR, and the mixture thereof; and dichloromethane, such as dichloromethane AR grade; and the mixture of ethanol and dichloromethane at any ratio. The preferred solvent is ethanol absolute GR.

The ammonio methacrylate copolymer used in the method of preparing a stable solid dispersion of prostaglandin drug in the present invention is in the range of from about 1 to about 1000 parts, preferably from about 10 to about 450 parts, based on 1 part of prostaglandin drug. The stable solid dispersion obtained from the method of the present invention is a sustained release type.

According to the preparation method of the present invention, the ammonio methacrylate copolymer used is selected from the group consisting of Eudragit RS (ammonio methacrylate copolymer, Type B, USP), Eudragit RL (ammonio methacrylate copolymer, Type A, USP), and the mixture thereof. Furthermore, the ammonio methacrylate copolymer may be selected from the group consisting of Eudragit S (methacrylic acid copolymer, Type B, USP), Eudragit L (methacrylic acid copolymer, Type A, USP), and the mixture thereof. Further detailed explanations and definitions about the Eudragit RS, Eudragit RL, Eudragit S, and Eudragit L are stated above.

In accordance with the present invention, the mixture in step (2) is stirred for about 1 hour to 3 hours, preferably for about 2 hours. The stirring is conducted under covering. Nitrogen or any other suitable gases can be used to blow-dry the residue in step (3). In step (4) of the present method, the solid dispersion is dried at a temperature of from 40° C. to 50° C. for from about 1 hour to 3 hours.

The resultant solid dispersion product is then stored at a temperature of from about -80° C. to 30° C., preferably from about -27° C. to 5° C. in an air tight container, with the protection of dry silica gel desiccators, prior to use.

Further, the present invention provides a method of preparing a stable solid dispersion of prostaglandin drug Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-

hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1-yl]heptanoate, comprising the following steps:

- (1) dissolving Misoprostol in a solvent to form a solution;
- (2) adding an ammonio methacrylate copolymer into the solution to form a mixture and stirring the mixture for a period of time;
- (3) flash evaporating the solvent and blow-drying a residue after evaporation to obtain a solid dispersion;
- (4) drying the solid dispersion; and
- (5) grinding and sieving the solid dispersion to obtain a resultant product.

The ammonio methacrylate copolymer used in the method of preparing a stable solid dispersion of Misoprostol in the present invention is in the range of from about 1 to about 1000 parts, preferably from about 10 to about 450 parts, based on 1 part of Misoprostol.

The solid dispersion of the present invention can be used directly as a powder form, or can be filled in capsules with or without pharmaceutical excipients, or can be compressed into tablets with or without additional excipients, or can be used to coat on an inert or active core to form pellets.

The following examples are offered by way of illustration. The examples are not intended to limit the scope of the invention in any respect and should not be so construed.

EXAMPLES

Example 1

This example is to prepare a stabilized, sustained release solid dispersion of Misoprostol, ($\pm$) methyl 7-[3(α)-hydroxy-2- β -(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1 α -yl]heptanoate, comprising Misoprostol and Eudragit RS (ammonio methacrylate copolymer, Type B, USP) at a ratio of 1:150.

66.7 mg of Misoprostol was dissolved in 47 ml of absolute ethanol. 20 g of Eudragit RS was added into the Misoprostol-ethanol solution to form a mixture of Misoprostol and Eudragit at a ratio of 1:150. The combined Misoprostol-Eudragit-ethanol solution mixture was stirred for 2 hours under covering. Then the solvent was flash evaporated and the residue was blow-dried with Nitrogen. The solid residue, i.e. the solid dispersion, was dried for 2 hours at 40° C. and subsequently the solid residue was ground, sieved through 40 mesh screen. The obtained powder form of the solid dispersion of Misoprostol and Eudragit RS should be stored in an air tight container.

Example 2

The steps of Example 1 were repeated, except that 40 g and 60 g of Eudragit RS were added into the Misoprostol-ethanol solution to form a stabilized, sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:300 and 1:450, respectively.

Example 3

The steps of Example 1 were repeated, except that 47 ml of a solvent containing 9 parts of absolute ethanol and 1 part of dichloromethane, and 40 g of Eudragit RS were used to form a stabilized, sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:300.

Example 4

The steps of Example 1 were repeated, except that 47 ml of dichloromethane and 40 g of Eudragit RS were used to form a stabilized, sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:300.

Example 5

The steps of Example 1 were repeated, except that three different amounts, i.e. 1.33 g, 2.67 g and 5.34 g of Eudragit

5

RS were used to form three stabilized, sustained release solid dispersions of Misoprostol and Eudragit at a ratio of 1:10, 1:20 and 1:40, respectively. After the solid residues, i.e., the solid dispersions were dried for about 2 hours at 40° C., the solid residues were ground and sieved through 100 mesh. The fine powder form of these solid dispersions were stored at a temperature of -27° C. in an air tight container with the protection of dry silica gel desiccators, prior to use.

Example 6

The steps of Example 5 were repeated, except that two different amounts, i.e., 6.67 g and 60 g of Eudragit RL were used to form a stabilized, sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:50 and 1:450, respectively.

Example 7

The steps of Example 5 were repeated, except that 6.67 g of Eudragit RS was used to form a stabilized, sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:50.

Example 8

The sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:50 obtained from Example 7 was used to prepare homogenous powder blends.

Seven homogenous powder blends were prepared by mixing the solid dispersion obtained from Example 7 with seven individual different pharmaceutical excipients at a ratio by weight as follows. One part of the sustained release solid dispersion was mixed with five parts of Avicel pH 102 (Microcrystalline cellulose), Eudragit RS, Corn Starch and Mannitol, respectively. Furthermore, fifty parts of the sustained release solid dispersion was mixed with two parts of Talc, Magnesium Stearate and Hydrogenated Castor Oil, respectively.

6

Example 9

The sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:50 obtained from Example 7 was used to prepare filled sustained release capsules.

20.4 mg of the solid dispersion obtained from Example 7 was weighed and filled into No. 2 gelatin capsules. Each sustained release capsule contained 400 µg of prostaglandin drug, Misoprostol.

Example 10

The sustained release solid dispersion of Misoprostol and Eudragit at a ratio of 1:50 obtained from Example 7 was used to prepare sustained release tablets.

20.4 mg of the solid dispersion obtained from Example 7, 167.6 mg of Avicel pH 102 (microcrystalline cellulose), 10.0 mg of sodium starch glycolate, and 2.0 mg of hydrogenated castor oil were mixed to prepare one sustained release tablet. The total weight of each sustained release tablet was 200 mg. Totally 2000 sustained release tablets were prepared. Each sustained release tablet contained 400 µg of prostaglandin drug, Misoprostol.

Example 11

The stability of Misoprostol in the solid dispersion of Examples 1 to 10 was determined after storing at various temperatures for different time periods. After assaying the percent potency remained of Misoprostol in each sample by high performance liquid chromatography (HPLC), the results were summarized in Table I for Examples 1-4, Table II for Examples 5 and 6, Table III for Example 8, and Table IV for Examples 7, 9 and 10, for a predetermined period at each temperature. All assay was done by using a Spectra-Physics Liquid Chromatography equipped with Model P2000 pump, AS 3000 autosampler, UV 1000 detector, IMS 1000 integrator and SN 4000 controller. The wave length of detector was set at 210 nm with a chart speed of 0.5 cm/min. Assay was achieved by using a Lichrospher 100, RP-8, 125x4 mm ID column, eluted with a mobile phase containing 45 parts of acetonitrile and 55 parts of pH 2.81 phosphate buffer in volume with a flow rate of 1 ml/minute.

TABLE I

Stability Data on Misoprostol Alone and Its Eudragit Solid Dispersions (% Potency Remained)									
Storage Temperature	5° C.			30° C.		50° C.		70° C.	
Storage Time (Week)	0	3	6	3	6	1	3	6	1
Misoprostol Alone	100	100	94	92.2	82.7	93.9	91.7	64	81.2
Ex. 1 (1:150 Ratio)	100	99.2	99.5	95.8	97.7	97.1	91.4	80.1	89.8
Ex. 2 (1:300 Ratio)	100	99.2	98.6	94.2	95.8	95.6	90.7	81.5	88.5
Ex. 2 (1:450 Ratio)	100	100	100	100	100	100	93	83.3	83
Ex. 3 (1:300 Ratio)	100	100	100	100	100	99.7	95.3	95.8	92.4
Ex. 4 (1:300 Ratio)	100	100	99.7	100	100	99.5	96.1	91.7	85.9

TABLE II

Stability Data on Misoprostol Alone and Its Eudragit Solid Dispersions (% Potency Remained)										
Storage Temperature	30° C.				50° C.				70° C.	
Storage Time (Week)	0	3	6	12	1	3	6	12	1	2
Misoprostol Alone	100	92.2	82.7	14.4	93.9	91.7	64	10.9	81.2	41.5
Ex. 5 (1:10 Ratio)	100	99.5	102.2	93.0	97.0	97.2	94.8	91.8	—	—
Ex. 5 (1:20 Ratio)	100	99.1	98.1	95.6	102	95.8	95.0	93.7	93.9	88.6
Ex. 5 (1:40 Ratio)	100	98.8	100.4	97.5	100.7	99.7	98.3	96.5	95.0	92.3
Ex. 6 (1:50 Ratio)	100	96.5	94.5	96.6	96.5	97.0	93.0	93.0	94.5	90.5
Ex. 6 (1:450 Ratio)	100	102.9	101.5	97	97.9	95.3	95.2	95.7	97.6	92.3

TABLE III-1

Stability Data of Misoprostol in Eudragit Solid Dispersions When Mixed with Seven Different Pharmaceutical Excipients in Ex. 8 (% Potency Remained)				
(Solid Dispersion:Excipients = 1.5)				
Ratio Excipients	Avicel pH102	Eudragit RS	Corn Starch	Mannitol
After 1 week at 70° C. Storage	102.6	97.7	100.6	97.3

TABLE III-2

Stability Data of Misoprostol in Eudragit Solid Dispersions When Mixed with Seven Different Pharmaceutical Excipients in Ex. 8 (% Potency Remained)			
(Solid Dispersion:Excipients 50:2)			
Ratio Excipients	Talc	Magnesium Stearate	Hydrogenated Castor Oil
After 1 week at 70° C. Storage	98.4	99.9	100.0

TABLE IV

Stability Data of Misoprostol on Its Sustained Release Solid Dispersion at 1:50 Ratio in Ex. 7, Its Sustained Release Tablets in Ex. 10, and Its Sustained Release Capsules in Ex. 9 (% Potency Remained)*									
Storage Relative Humidity (RH) and Temperature	75% RH +37° C.			75% RH +43° C.			75% RH +50° C.		
	1	3	6	1	3	6	1	3	6
Storage Time (Month)									
Misoprostol-Eudragit Solid Dispersion (1:50 Ratio)	95.1	95.9	92.1	96.0	94.7	90.1	93.5	90.7	76
Sustained Release Tablets	100.0	96.6	97.3	100.0	96.4	91.6	93.8	89.6	56.8
Sustained Release Capsules	97.9	—	95.4	95.3	—	92.2	92.8	—	68.8

*An air tight polyethylene container was used for this stability study.

The stability of the solid dispersion of Misoprostol of the present invention, and the capsules and the tablets prepared therefrom is tested after storing at various temperatures for different time periods. It is found that the present invention is capable of providing a stabilized, solid dispersion of Misoprostol, (±) methyl 7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl] heptanoate. Furthermore, according to the present invention, the capsules filled with the stabilized, solid dispersion of Misoprostol or the tablets compressed from the stabilized solid dispersion of Misoprostol are stable and sustained release type.

Example 12

The sustained release dissolution profile of Misoprostol-Eudragit solid dispersion at the ratio of 1:50 obtained from Example 7 and its sustained release tablets obtained from Example 10 were generated by using a USP paddle dissolution tester at 37° C. with an agitation speed of 75 rpm. The

sustained release dissolution profile were shown in FIGS. 1 (Example 7) and 2 (Example 10). Specifically, the dissolution testing in FIG. 1 was conducted in 0.2% sodium lauryl sulfate (SLS) dissolution medium.

At each time point, dissolution samples were assayed by the high performance liquid chromatography (HPLC) method described in Example 11. A typical dissolution profile of a commercial available Misoprostol immediate release tablet, known as Cytotec which contains 0.2 mg Misoprostol, was shown on FIG. 3 for the purpose of comparison.

From FIGS. 1, 2 and 3, it is clear that the sustained release effect of the solid dispersion of Misoprostol of the present invention is better than that of commercial available, Misoprostol immediate release tablet. In accordance with the present invention, only one tablet or capsule produced from the solid dispersion of Misoprostol might be all it needed in one day since the solid dispersion of Misoprostol is sustained release type.

While the invention has been described with respect to certain preferred exemplifications and embodiments, it is not intended to limit the scope of the invention thereby, but solely by the claims appended hereto.

We claim:

1. A stable solid dispersion of Misoprostol in powder form comprising from about 1 to about 1000 parts of an ammonio methacrylate copolymer and about 1 part of Misoprostol, (±)methyl 7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl]heptanoate.

2. A stable solid dispersion according to claim 1, comprising from about 10 to about 450 parts of the ammonio methacrylate copolymer.

3. A stable solid dispersion according to claim 1 being a sustained release solid dispersion.

4. A stable solid dispersion according to claim 1, wherein the ammonio methacrylate copolymer is selected from the group consisting of ammonio methacrylate copolymer, Type B (Eudragit RS), ammonio methacrylate copolymer, Type A (Eudragit RL), and mixtures thereof.

5. A solid dispersion according to claim 4, wherein the ammonio methacrylate copolymer, Type B (Eudragit RS) is selected from the group consisting of powders of ammonio methacrylate copolymer, Type B (Eudragit RSPM), fine powders of ammonio methacrylate copolymer, Type B (Eudragit RSPO), granules of ammonio methacrylate copolymer, Type B (Eudragit RS100), ammonio methacrylate copolymer, Type B dissolved in an organic solvent (Eudragit RS12.5), and mixtures thereof.

6. A solid dispersion according to claim 4, wherein the ammonio methacrylate copolymer, Type B (Eudragit RS)

has any molar ratio of ammonium groups to (meth)acrylic acid ester groups.

7. A solid dispersion according to claim 4, wherein the ammonio methacrylate copolymer, Type B (Eudragit RS) has a molar ratio of ammonium groups to (meth)acrylic acid ester groups of 1:40.

8. A solid dispersion according to claim 4, wherein the ammonio methacrylate copolymer, Type A (Eudragit RL) is selected from the group consisting of powders of ammonio methacrylate copolymer, Type A (Eudragit RLPM), fine powders of ammonio methacrylate copolymer, Type A (Eudragit RLPO), granules of ammonio methacrylate copolymer, Type A (Eudragit RL100), ammonio methacrylate copolymer, Type A dissolved in an organic solvent (RL12.5), and mixtures thereof.

9. A solid dispersion according to claim 4, wherein the ammonio methacrylate copolymer, Type A (Eudragit RL) has any molar ratio of ammonium groups to (meth)acrylic acid ester groups.

10. A solid dispersion according to claim 4, wherein the ammonio methacrylate copolymer, Type A (Eudragit RL) has a molar ratio of ammonium groups to (meth)acrylic acid ester groups of 1:20.

11. A solid dispersion according to claim 1, wherein the ammonio methacrylate copolymer is selected from the group consisting of methacrylic acid copolymer, Type B (Eudragit S), methacrylic acid copolymer, Type A (Eudragit L), and mixtures thereof.

12. A method of preparing a stable solid dispersion of Misoprostol in powder form comprising:

- (1) dissolving Misoprostol in a solvent to form a solution;
- (2) adding an ammonio methacrylate copolymer into the solution to form a mixture and stirring the mixture for a period of time, wherein the ammonio methacrylate copolymer is added in an amount of from about 10 to about 450 parts based on 1 part of Misoprostol;
- (3) flash evaporating the solvent and blow-drying a residue after evaporation to obtain a solid dispersion;
- (4) drying the solid dispersion; and
- (5) grinding and sieving the solid dispersion.

13. A method according to claim 12, wherein the solvent is selected from the group consisting of ethanol, dichloromethane, and the mixture thereof.

14. A method according to claim 13, wherein the ethanol is selected from the group consisting of ethanol 200 proof grade, ethanol 3A grade, ethanol USP, ethanol absolute GR, and the mixtures thereof.

15. A method according to claim 12, wherein the solvent is ethanol absolute GR.

16. A method according to claim 13, wherein the dichloromethane is dichloromethane AR grade.

17. A method according to claim 12, wherein the ammonio methacrylate copolymer is selected from the group consisting of ammonio methacrylate copolymer, Type B (Eudragit RS), ammonio methacrylate copolymer, Type A (Eudragit RL), and mixtures thereof.

18. A method according to claim 17, wherein the ammonio methacrylate copolymer, Type B, (Eudragit RS) is selected from the group consisting of powders of ammonio methacrylate copolymer, Type B (Eudragit RSPM), fine powders of ammonio methacrylate copolymer, Type B (Eudragit RSPO), granules of ammonio methacrylate copolymer, Type B (Eudragit RS100), ammonio methacrylate copolymer, Type B dissolved in an organic solvent (Eudragit RS12.5), and mixtures thereof.

19. A method according to claim 17, wherein the ammonio methacrylate copolymer, Type A (Eudragit RL) is selected from the group consisting of powders of ammonio methacrylate copolymer, Type A (Eudragit RLPM), fine powders of ammonio methacrylate copolymer, Type A (Eudragit RLPO), granules of ammonio methacrylate copolymer, Type A (Eudragit RL100), ammonio methacrylate copolymer, Type A dissolved in an organic solvent (Eudragit RL12.5), and mixtures thereof.

20. A method according to claim 12, wherein the ammonio methacrylate copolymer is selected from the group consisting of methacrylic acid copolymer, Type B (Eudragit S), methacrylic acid copolymer, Type A (Eudragit L), and mixtures thereof.

21. A method according to claim 12, wherein the mixture in step (2) is stirred for about 1 hour to about 3 hours.

22. A method according to claim 21, wherein the mixture in step (2) is stirred for about 2 hours.

23. A method according to claim 12, wherein the solid dispersion is dried at a temperature of from 40° C. to 50° C.

24. A method according to claim 12, wherein the solid dispersion is dried for from about 1 hour to about 3 hours.

* * * * *



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(54) **BENZIMIDAZOLE COMPOUND CRYSTAL**

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(57) **ABSTRACT**

A novel crystal of (R)-2-[[[3-methyl-4-(2, 2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof of the present invention is useful for an excellent antiulcer agent.

8 Claims, No Drawings

BENZIMIDAZOLE COMPOUND CRYSTAL

This application is the National Stage of International Application No. PCT/JP00/03881, filed on Jun. 15, 2000.

TECHNICAL FIELD

The present invention relates to a crystal of a benzimidazole compound showing antiulcer action.

BACKGROUND ART

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof having an antiulcer action is reported in JP-A-61-50978, etc.

There is a demand for a more stable and excellently absorbable antiulcer agent.

DISCLOSURE OF INVENTION

Having chiral sulfurin themolecular structure thereof, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole occurs in two kinds of optical isomers. After extensive exploration, the present inventors succeeded in optically resolving and crystallizing the (R)-isomer of 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, for the first time found that this crystal serves satisfactorily as a pharmaceutical, made further investigation based on this finding, and developed the present invention.

Accordingly, the present invention relates to:

- [1] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof;
- [2] a crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole;
- [3] a crystal according to the above [2] wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom;
- [4] a pharmaceutical composition which comprises the crystal according to the above [1];
- [5] a pharmaceutical composition according to the above [4], which is for treating or preventing digestive ulcer;
- [6] a method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to the above [1] with a pharmaceutically acceptable excipient, carrier or diluent;
- [7] use of the crystal according to the above [1] for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer, and so forth.

The "salt" of "(R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof" includes, for example, metal salts, salts with organic bases, salts with basic amino acids, and so forth. Preferred are physiologically acceptable salts.

Metal salts include, for example, alkali metal salts such as sodium salt and potassium salt; and alkaline earth metal salts such as calcium salt, magnesium salt and barium salt. Salts with organic bases include, for example, salts with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, N,N-dibenzylethylenediamine, etc. Salts with basic amino acids include, for example, salts with arginine, lysine, etc.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof may be a hydrate or not.

Said "hydrate" includes 0.5 hydrate to 5.0 hydrate. Among others, 0.5 hydrate, 1.0 hydrate, 1.5 hydrate, 2.0 hydrate and 2.5 hydrate are preferred. More preferred is 1.5 hydrate.

The crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluorobethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof can be produced by subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof to an optical resolution or subjecting 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]thio]-1H-benzimidazole to an asymmetrical oxidization to obtain the (R)-isomer, followed by crystallizing the resultant isomer.

Methods of optical resolution include per se known methods, for example, a fractional recrystallization method, a chiral column method, a diastereomer method, and so forth. Asymmetric oxidation includes per se known methods.

The "fractional recrystallization method" includes a method in which a salt is formed between a racemate and an optically active compound [e.g., (+)-mandelic acid, (-)-mandelic acid, (+)-tartaric acid, (-)-tartaric acid, (+)-1-phenethylamine, (-)-1-phenethylamine, cinchonine, (-)-cinchonidine, brucine, etc.], which salt is separated by fractional recrystallization etc., and, if desired, subjected to a neutralization process, to give a free optical isomer.

The "chiral column method" includes a method in which a racemate or a salt thereof is applied to a column for optical isomer separation (chiral column). In the case of liquid chromatography, for example, optical isomers are separated by adding a racemate to a chiral column such as ENANTIO-OVM (produced by Tosoh Corporation) or the DAICEL CHIRAL series (produced by Daicel Corporation), and developing the racemate in water, a buffer (e.g., phosphate buffer), an organic solvent (e.g., hexane, ethanol, methanol, isopropanol, acetonitrile, trifluoroacetic acid, diethylamine, triethylamine, etc.), or a solvent mixture thereof. In the case of gas chromatography, for example, a chiral column such as CP-Chirasil-DeX CB (produced by GL Science) is used to separate optical isomers.

The "diastereomer method" includes a method in which a racemate and an optically active reagent are reacted (preferably, an optically active reagent is reacted to the 1-position of the benzimidazole group) to give a diastereomer mixture, which is then subjected to ordinary separation means (e.g., fractional recrystallization, chromatography, etc.) to obtain either diastereomer, which is subjected to a chemical reaction (e.g., acid hydrolysis, base hydrolysis, hydrogenolysis, etc.) to cut off the optically active reagent moiety, whereby the desired optical isomer is obtained. Said "optically active reagent" includes, for example, an optically active organic acids such as MTPA [a-methoxy-a-(trifluoromethyl)phenylacetic acid] and (-)-menthoxyacetic acid; and optically active alkoxymethyl halides such as (1R-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane, etc.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof is produced by the methods described in JP-A-61-50978, U.S. Pat. No. 4,628,098 etc. or analogous methods thereto.

Methods of crystallization includes per se known methods, for example, a crystallization from solution, a crystallization from vapor, and a crystallization from molten form.

Methods of the "crystallization from solution" include, for example, a concentration method, a slow cooling method, a reaction method (diffusion method, electrolysis method), a hydrothermal growth method, a fusing agent method, and so forth. Solvents to be used include, for example, aromatic hydrocarbons (e.g., benzene, toluene, xylene, etc.), pharmaceutical composition with good repro-

ducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax (maximum blood concentration) and a greater AUC (area under the concentration-time curve) than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low doses and with a low prevalence of adverse reactions.

The crystal of the present invention is useful in mammals (e.g., humans, monkeys, sheep, bovines, horses, dogs, cats, rabbits, rats, mice, etc.) for the treatment and prevention of digestive ulcer (e.g., gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, reflux esophagitis, NUD (non-ulcer dyspepsia), gastric cancer and gastric MALT lymphoma; *Helicobacter pylori* eradication; suppression of upper gastrointestinal hemorrhage due to digestive ulcer, acute stress ulcer and hemorrhagic gastritis; suppression of upper gastrointestinal hemorrhage due to invasive stress (stress from major surgery necessitating intensive management after surgery, and from cerebral vascular disorder, head trauma, multiple organ failure and extensive burns necessitating intensive treatment); treatment and prevention of ulcer caused by a nonsteroidal anti-inflammatory agent; treatment and prevention of hyperacidity and ulcer due to postoperative stress; pre-anesthetic administration etc.

The crystal of the present invention is of low toxicity, and can be safely administered orally or non-orally (e.g., topical, rectal and intravenous administration, etc.), as such or in the form of pharmaceutical compositions formulated with a pharmacologically acceptable carrier, e.g.; tablets halogenated hydrocarbons (e.g., dichloromethane, chloroform, etc.), saturated hydrocarbons (e.g., hexane, heptane, cyclohexane, etc.), ethers (e.g., diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, etc.), nitriles (e.g., acetonitrile, etc.), ketones (e.g., acetone, etc.), sulfoxides (e.g., dimethylsulfoxide, etc.), acid amides (e.g., N,N-dimethylformamide, etc.), esters (e.g., ethyl acetate, etc.), alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), water, and so forth. These solvents may be used singly or in mixtures of two or more kinds in appropriate ratios (e.g., 1:1 to 1:100).

Methods of the "crystallization from vapor" include, for example, a gasification method (sealed tube method, gas stream method), a gas phase reaction method, a chemical transportation method, and so forth.

Methods of the "crystallization from molten form" include, for example, a normal freezing method (pulling-up method, temperature gradient method, Bridgman method), a zone melting method (zone leveling method, float zone method), a special growth method (VLS method, liquid phase epitaxis method), and so forth.

For analyzing the crystal obtained, X-ray diffraction crystallographic analysis is commonly used. In addition, crystal orientation can also be determined by a mechanical method, an optical method, etc.

A thus obtained crystal of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole or a salt thereof (hereinafter also referred to as "crystal of the present invention") is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion-inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action, etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid (including sugar-coated tablets and film-coated tablets), powders, granules, capsules (including soft capsules), orally disinte-

grating tablets, liquids, injectable preparations, suppositories, sustained-release preparations and patches, in accordance with a commonly known method.

The content of the crystal of the present invention in the pharmaceutical composition of the present invention is about 0.01 to 100% by weight relative to the entire composition. Varying depending on subject of administration, route of administration, target disease etc., its dose is normally about 0.5 to 1,500 mg/day, preferably about 5 to 150 mg/day, based on the active ingredient, for example, when it is orally administered as an antiulcer agent to an adult human (60 kg). The crystal of the present invention may be administered once daily or in 2 to 3 divided portions per day.

Pharmacologically acceptable carriers that may be used to produce the pharmaceutical composition of the present invention include various organic or inorganic carrier substances in common use as pharmaceutical materials, including excipients, lubricants, binders, disintegrants; water-soluble polymers and basic inorganic salts for solid preparations; and solvents, dissolution aids, suspending agents, isotonicizing agents, buffers and soothing agents for liquid preparations. Other ordinary pharmaceutical additives such as preservatives, antioxidants, coloring agents, sweetening agents, souring agents, bubbling agents and flavorings may also be used as necessary.

Such "excipients" include, for example, lactose, sucrose, D-mannitol, starch, cornstarch, crystalline cellulose, light silicic anhydride and titanium oxide.

Such "lubricants" include, for example, magnesium stearate, sucrose fatty acid esters, polyethylene glycol, talc and stearic acid.

Such "binders" include, for example, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, crystalline cellulose, α -starch, polyvinylpyrrolidone, gum arabic powder, gelatin, pullulan, and low-substitutional hydroxypropyl cellulose.

Such "disintegrants" include (1) crosslinked povidone, (2) what is called super-disintegrants such as crosslinked carmellose sodium (FMC-Asahi Chemical) and carmellose calcium (Gotoku Yakuhin), (3) carboxymethyl starch sodium (e.g., product of Matsutani Chemical), (4) low-substituted hydroxypropyl cellulose (e.g., product of Shin-Etsu Chemical), (5) cornstarch, and so forth. Said "crosslinked povidone" may be any crosslinked polymer having the chemical name 1-ethenyl-2-pyrrolidinone homopolymer, including polyvinylpyrrolidone (PVPP) and 1-vinyl-2-pyrrolidinone homopolymer, and is exemplified by Colidon CL (produced by BASF), Polyplasdon XL (produced by ISP), Polyplasdon XL-10 (produced by ISP) and Polyplasdon INF-10 (produced by ISP).

Such "water-soluble polymers" include, for example, ethanol-soluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropyl cellulose (hereinafter also referred to as HPC), polyvinylpyrrolidone] and ethanol-insoluble water-soluble polymers [e.g., cellulose derivatives such as hydroxypropylmethyl cellulose (hereinafter also referred to as HPMC), methyl cellulose and carboxymethyl cellulose sodium, sodium polyacrylate, polyvinyl alcohol, sodium alginate, guar gum].

Such "basic inorganic salts" include, for example, basic inorganic salts of sodium, potassium, magnesium and/or calcium. Preferred are basic inorganic salts of magnesium and/or calcium. More preferred are basic inorganic salts of magnesium. Such basic inorganic salts of sodium include, for example, sodium carbonate, sodium hydrogen carbonate, disodium hydrogenphosphate, etc. Such basic inorganic salts of potassium include, for example, potassium carbonate, potassium hydrogen carbonate, etc. Such basic inorganic salts of magnesium include, for example, heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, magnesium metasilicate

aluminate, magnesium silicate, magnesium aluminate, synthetic hydrotalcite [$\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3\cdot 4\text{H}_2\text{O}$], alumina hydroxide magnesium, and so forth. Among others, preferred is heavy magnesium carbonate, magnesium carbonate, magnesium oxide, magnesium hydroxide, etc. Such basic inorganic salts of calcium include, for example, precipitated calcium carbonate, calcium hydroxide, etc.

Such "solvents" include, for example, water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil and olive oil.

Such "dissolution aids" include, for example, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate and sodium citrate.

Such "suspending agents" include, for example, surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and monostearic glycerol; and hydrophilic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose.

Such "isotonizing agents" include, for example, glucose, D-sorbitol, sodium chloride, glycerol and D-mannitol.

Such "buffers" include, for example, buffer solutions of phosphates, acetates, carbonates, citrates etc.

Such "soothing agents" include, for example, benzyl alcohol.

Such "preservatives" include, for example, p-oxybenzoic acid esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid and sorbic acid.

Such "antioxidants" include, for example, sulfites, ascorbic acid and α -tocopherol.

Such "coloring agents" include, for example, food colors such as Food Color Yellow No. 5, Food Color Red No. 2 and Food Color Blue No. 2; and food lake colors and red oxide.

Such "sweetening agents" include, for example, saccharin sodium, dipotassium glycyrrhetinate, aspartame, stevia and thaumatin.

Such "souring agents" include, for example, citric acid (citric anhydride), tartaric acid and malic acid.

Such "bubbling agents" include, for example, sodium bicarbonate.

Such "flavorings" may be synthetic substances or naturally occurring substances, and include, for example, lemon, lime, orange, menthol and strawberry.

The crystal of the present invention may be prepared as a preparation for oral administration in accordance with a commonly known method, by, for example, compression-shaping it in the presence of an excipient, a disintegrant, a binder, a lubricant, or the like, and subsequently coating it as necessary by a commonly known method for the purpose of taste masking, enteric dissolution or sustained release. For an enteric preparation, an intermediate layer may be provided by a commonly known method between the enteric layer and the drug-containing layer for the purpose of separation of the two layers.

For preparing the crystal of the present invention as an orally disintegrating tablet, available methods include, for example, a method in which a core containing crystalline cellulose and lactose is coated with the crystal of the present invention and a basic inorganic salt, and is further coated with a coating layer containing a water-soluble polymer, to give a composition, which is coated with an enteric coating layer containing polyethylene glycol, further coated with an enteric coating layer containing triethyl citrate, still further coated with an enteric coating layer containing polyethylene glycol, and still yet further coated with mannitol, to give fine granules, which are mixed with additives and shaped. The above-mentioned "enteric coating layer" includes, for example, aqueous enteric polymer substrates such as cellulose acetate phthalate (CAP), hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, methacrylic acid copolymers (e.g., Eudragit L30D-55 (trade name; produced by Rohm), Colicoat MAE30DP (trade name; produced by BASF), Polyquid PA30 (trade name; produced by San-yo Chemical)), carboxymethylethyl cellulose and shellac; sustained-release substrates such as methacrylic acid polymers (e.g., Eudragit NE30D (trade name), Eudragit RL30D (trade name), Eudragit RS30D (trade name); etc.); water-soluble polymers; plasticizers such as triethyl citrate, polyethylene glycol, acetylated monoglycerides, triacetin and castor oil; and mixtures thereof. The above-mentioned "additive" includes, for example, water-soluble sugar alcohols (e.g., sorbitol, mannitol, maltitol, reduced starch saccharides, xylitol, reduced palatinose, erythritol, etc.), crystalline cellulose (e.g., Ceolac KG 801, Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302, Avicel RC-591 (crystalline cellulose carmellose sodium)), low-substituted hydroxypropyl cellulose (e.g., LH-22, LH-32, LH-23, LH-33 (Shin-Etsu Chemical) and mixtures thereof); binders, souring agents, bubbling agents, sweetening agents, flavorings, lubricants, coloring agents, stabilizers, excipients, disintegrants etc. are also used.

The crystal of the present invention may be used in combination with 1 to 3 other active ingredients.

Such "other active ingredients" include, for example, anti-*Helicobacter pylori* activity substances, imidazole compounds, bismuth salts, quinolone compounds, and so forth. Of these substances, preferred are anti-*Helicobacter pylori* action substances, imidazole compounds etc. Such "anti-*Helicobacter pylori* action substances" include, for example, antibiotic penicillins (e.g., amoxicillin, benzylpenicillin, piperacillin, mecillinam, etc.), antibiotic cefems (e.g., cefixime, cefaclor, etc.), antibiotic macrolides (e.g., erythromycin, clarithromycin, etc.), antibiotic tetracyclines (e.g., tetracycline, minocycline, streptomycin, etc.), antibiotic aminoglycosides (e.g., gentamicin, amikacin, etc.), imipenem, and so forth. Of these substances, preferred are antibiotic penicillins, antibiotic macrolides etc. Such "imidazole compounds" include, for example, metronidazole, miconazole, etc. Such "bismuth salts" include, for example, bismuth acetate, bismuth citrate, etc. Such "quinolone compounds" include, for example, ofloxacin, ciprofloxacin, etc.

Such "other active ingredients" and the crystal of the present invention may also be used in combination as a mixture prepared as a single pharmaceutical composition [e.g., tablets, powders, granules, capsules (including soft capsules), liquids, injectable preparations, suppositories, sustained-release preparations, etc.], in accordance with a commonly known method, and may also be prepared as separate preparations and administered to the same subject simultaneously or at a time interval.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is hereinafter described in more detail by means of, but is not limited to, the following reference examples, examples and experimental examples.

In the following reference examples and examples, the term "room temperature" indicates about 15 to 30° C.

Melting points were measured using the Micro Melting Point Apparatus (produced by Yanagimoto Seisakusho), and uncorrected values are shown.

¹H-NMR spectra were determined with CDCl_3 as the solvent using Varian Gemini-200; data are shown in chemical shift δ (ppm) from the internal standard tetramethylsilane.

IR was determined using SHIMADZU FTIR-8200.
UV was determined using the HITACHI U-3200 spectro-
photometer.

Optical rotation $[\alpha]_D$ was determined at 20° C. using the
DIP-370 digital polarimeter (produced by JASCO).

Optical purity was determined by HPLC (column:
CHIRALCEL OD 4.6 mm dia.×250 mm, temperature: about
20° C., mobilephase: hexane/2-propanol=80/20 or hexane/
2-propanol=85/15, flow rate: 1.0 ml/min, detection wave-
length: 285 nm) using a chiral column.

Crystal X-ray diffraction data for determining the absolute
structure of sulfoxide were obtained by means of a 4-circle
diffractometer (RIGAKU AFC5R) using the Cu-K α ray.
After the initial phase was determined by the direct method,
the fine structure was analyzed using SHELXL-93. X-ray
powder diffraction was determined using the X-ray Powder
Diffraction meter Rigaku RINT2500 (ultraX18) No. PX-3.

The other symbols used herein have the following defi-
nitions:

- s: singlet
- d: doublet
- t: triplet
- q: quartet
- m: multiplet
- bs: broad singlet
- J: binding constant

EXAMPLES

Reference Example 1

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-
pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-
Lansoprazole)

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]
methyl]sulfinyl]-1H-benzimidazole (lansoprazole)
(racemate) (3.98 g) was dissolved in the following mobile
phase (330 ml) and acetonitrile (37 ml) and fractionated by
HPLC (column: CHIRALCEL OD 20 mm dia.×250 mm,
temperature: 30° C., mobile phase: hexane/2-propanol/
ethanol=255/35/10, flowrate: 16 ml/min, detection wave-
length: 285 nm, 1 shot: 20–25 mg). Fractions of optical
isomers of shorter retention time were combined and con-
centrated; the individual lots were combined and dissolved
in ethanol and filtered through a 0.45 μ m filter; after hexane
was added, the filtrate was again evaporated to dryness to
yield R(+)-lansoprazole (1.6 g, optical purity>97.6%ee) as
an amorphous substance.

The amorphous substance obtained was subjected to
fractionation and isolation in the same manner as above to
yield R(+)-lansoprazole.(1.37 g, optical purity>99.9%ee) as
an amorphous substance.

$[\alpha]_D^{25} = +174.3^\circ (c = 0.994\%, \text{CHCl}_3)$

Reference Example 2

Isolation of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-
pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-
Lansoprazole)

Lansoprazole (racemate) (34.2 g) was dissolved in
2-propanol (1,710 ml) and hexane (1,140 ml) containing
triethylamine (0.2%) and fractionated by HPLC (column:
CHIRALCEL OD 50 mm dia. ×500 mm, temperature: room
temperature, mobile phase: hexane/2-propanol=85/15, flow
rate: 60 ml/min, detection wavelength: 285 nm, single
injection: about 300 mg) to isolate the individual optical
isomers. Fractions of an optical isomer of shorter retention
time were combined and concentrated; the individual lots
were combined and dissolved in ethanol (250 ml); after

triethylamine (3 ml) was added, the solution was filtered
through a 0.45 μ m filter. After the filtrate was concentrated,
hexane was added, and the filtrate was again evaporated to
dryness to yield R(+)-lansoprazole (9.31 g, optical purity
98.3%ee) as an amorphous substance.

Reference Example 3

Production of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-
2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-
Lansoprazole)

10 In a nitrogen atmosphere, 2-[[[3-methyl-4-(2,2,2-
trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (20.0
g, 0.057 mol), toluene (100 ml), water (55 mg, 0.0031 mol
as based on total water content) and diethyl (+)-tartrate (2.12
ml, 0.012 mol) were mixed and stirred at 50 to 55° C. for 30
minutes. After titanium (IV) isopropoxide (1.66 ml, 0.0057
mol) was added to the mixture in a nitrogen atmosphere, the
mixture was stirred at 50 to 55° C. for 1 hour. After
diisopropylethylamine (3.25 ml, 0.019 mol) was added to
the resulting mixed liquor under cooling in a nitrogen
atmosphere, cumene hydroperoxide (30.6 ml, content 82%,
0.17 mol) was added at 0 to 5° C., followed by 3.5 hours of
stirring at 0 to 5° C., to cause the reaction.

Analysis of the reaction liquor by HPLC (column:
CHIRALCEL OD (Daicel Chemical Industries, Ltd.),
mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min,
detection wavelength: 285 nm) detected a sulfide at 1.32%
and a sulfone at 1.81% as related substances in the reaction
liquor, with no other related substances detected. The enan-
tiomer excess rate of the title compound in said reaction
liquor was 96.4%ee.

Reference Example 4

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-
pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-
Lansoprazole)

35 (1) In a nitrogen stream, 2-[[[3-methyl-4-(2,2,2-
trifluoroethoxy)-2-pyridyl]methyl]thio]benzimidazole (4.5
kg, 12.7 mol, containing 1.89 g of water), toluene (22 l),
water (25 g, 1.39 mol, or 1.49 mol if based on total water
content) and diethyl (+)-tartrate (0.958 l, 5.60 mol) were
mixed. In a nitrogen stream, titanium (IV) isopropoxide
(0.747 l, 2.53 mol) was added to this mixture at 50 to 60° C.,
and the mixture was stirred at the above temperature for 30
minutes. After diisopropylethylamine (0.733 l, 4.44 mol)
was added to the resulting mixed liquor at room temperature
in a nitrogen stream, cumene hydroperoxide (6.88 l, content
82%, 37.5 mol) was added at -5 to 5° C., followed by 1.5
hours of stirring at -5 to 5° C., to yield a reaction liquor.

Analysis of the reaction liquor by HPLC (column: Capcell
Pak (Shiseido, Co. Ltd.), mobile phase: solvent mixture
(acetonitrile/water/triethylamine=50/50/1); adjusted to pH
7.0 with phosphoric acid, flow rate: 1.0 ml/min, detection
wavelength: 285 nm) detected a sulfide at 1.87% and a
sulfone at 1.59% as related substances in the reaction liquor,
with no other related substances detected.

(2) To the reaction liquor obtained in (1) above, a 30%
aqueous solution of sodium thiosulfate (17 l) was added, in
a nitrogen stream, to decompose the residual cumene hydro-
peroxide. To the organic layer obtained by liquid separation,
water (4.5 l), heptane (13.5 l), t-butyl methyl ether (18 l) and
heptane (27 l) were added sequentially in this order, and this
mixture was stirred to cause crystallization. The resulting
crystal was separated and washed with t-butyl methyl ether-
toluene (t-butyl methyl ether:toluene=4:1) (4 l) to yield a
wet crystal of (R)-lansoprazole having the following powder
X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this
wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern
with characteristic peaks appearing at powder X-ray diffrac-

tion interplanar spacings (d) of 5.85, 4.70, 4.35, 3.66 and 3.48 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected a sulfone at 0.90% as a related substance in the crystal, with no sulfide or any other related substance detected. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(3) With stirring, a suspension in acetone (20 l) of 10 the wet crystal obtained in (2) above was added drop by drop into a mixed liquor of acetone (7 l) and water (34 l), then water (47 l) was added. The precipitated crystal was separated and washed with acetone-water (acetone:water=1:3) (4 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.)i mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(4) After the wet crystal obtained in (3) above was dissolved in ethyl acetate (45 l) and water (3 l), this solution was divided into liquid layers. The trace amount of insoluble matter in the organic layer was filtered off, then triethylamine (0.2 l) was added, after which the filtrate was concentrated under reduced pressure to a liquid volume of about 7 l. To this concentrate, methanol (2.3 l), about 12.5% aqueous ammonia at about 50° C. (23 l) and t-butyl methyl ether at about 50° C. (22 l) were added, and this liquid was divided into layers. To the organic layer, about 12.5% aqueous ammonia (11 l) was added, and this liquid was divided into layers (this operation was repeated once again). The water layers were combined, and ethyl acetate (22 l) was added, and then acetic acid was added drop by drop to reach a pH of about 8 under cooling. The liquid was divided into layers, and the water layer was extracted with ethyl acetate (11 l). The organic layers were combined and washed with about 20% saline (11 l). After triethylamine (0.2 l) was added, the organic layer was concentrated under reduced pressure. Acetone (5 l) was added to the concentrate, and this mixture was concentrated under reduced pressure. The concentrate was dissolved in acetone (9 l), and this solution was added drop by drop into a mixed liquor of acetone (4.5 l) and water (22.5 l), and then water (18 l) was added drop by drop to the mixed liquor obtained. The precipitated crystal was separated and washed sequentially with cold acetone-water (acetone:water=1:3) (3 l) and water (12 l) to yield a wet crystal of (R)-lansoprazole having the following powder X-ray diffraction interplanar spacings (d).

The results of powder X-ray diffraction analysis of this wet crystal are shown below.

The wet crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 8.33, 6.63, 5.86 and 4.82 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

(5) The wet crystal obtained in (4) above was dissolved in ethyl acetate (32 l). The water layer was separated by a

liquid separation procedure, and the organic layer obtained was concentrated under reduced pressure to a liquid volume of about 14 l. To the residual liquid, ethyl acetate (36 l) and activated charcoal (270 g) were added, after stirring, the activated charcoal was removed by filtration. The filtrate was concentrated under reduced pressure to a liquid volume of about 14 l. At about 40° C., heptane (90 l) was added drop by drop to the residual liquid. After stirring at the above temperature for about 30 minutes, the resulting crystal was separated, washed with about 40° C. ethyl acetate-heptane (ethyl acetate:heptane=1:8) (6 l), and dried to yield 3.4 kg of the title compound.

The results of powder X-ray diffraction analysis of this crystal are shown below.

The crystal yielded a powder X-ray diffraction pattern with characteristic peaks appearing at powder X-ray diffraction interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.

Analysis of this crystal by HPLC (column: CHIRALCEL OD (Daicel Chemical Industries, Ltd.), mobile phase: hexane/ethanol=90/10, flow rate: 1.0 ml/min, detection wavelength: 285 nm) detected no sulfone, sulfide or any other related substance in the crystal. The (R)-lansoprazole enantiomer excess rate in this crystal was 100%ee.

Example 1

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous R(+)-lansoprazole as obtained in Reference Example 1 (100 mg) was dissolved in acetonitrile (1 ml), which was gradually evaporated at room temperature in a nitrogen stream. After a crystal began to form, diethyl ether (1.5 ml) was added and the container was stoppered and kept standing at room temperature.

The crystal thus formed was subjected to X-ray structural analysis, and the absolute configuration of sulfoxide was found to be the R-configuration by a method using a Flack parameter. The remaining portion of the crystal was collected by filtration, twice washed with diethyl ether (1 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (38 mg).

m.p.: 144.0–144.5° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66; Found: C: 52.08, H: 3.76, N: 11.58, S: 8.75, F: 15.42; ¹H-NMR: 2.25 (3H, s), 4.40 (2H, q, J=7.8 Hz), 4.68 (1H, d, J=13.8 Hz), 4.85 (1H, d, J=13.8 Hz), 6.69 (1H, d, J=6.0 Hz), 7.29–7.39 (2H, m), 7.52 (1H, m), 7.81 (1H, m), 8.37 (1H, d, J=6.0 Hz), 11.00 (1H, bs). IR(v_{cm⁻¹}): 3081, 3042, 2984, 1586, 1478, 1441, 1306, 1267, 1163. UVmax(CHCl₃): 283.7 nm; [α]_D²⁰=+199.2° (c=0.202%, CHCl₃).

TABLE 1

Crystal Data and Structure Refinement Parameters	
Molecular formula:	C ₁₆ H ₁₄ N ₃ O ₂ F ₃ S
Molecular weight:	369.36
Crystal color, habit:	Colorless, tabular
Crystal Dimension:	0.40 × 0.30 × 0.04 (mm)
Crystal system:	Monoclinic
Lattice constants:	a = 8.549(1) (Å) b = 23.350(1) (Å) c = 8.720(2) (Å) β 32 103.90(1) (°) v = 1,689.8(4) (Å ³)
Space group:	P2 ₁
Z:	4
Density (calculated):	1.452 (g/cm ³)

TABLE 1-continued

Crystal Data and Structure Refinement Parameters	
Effective reflection:	9.12
number/parameter number:	
R ($I \geq 2\sigma(I)$):	0.036
Flack parameter:	-0.02(2)

Example 2

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole)

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 2 (9.17 g) was dissolved in acetone (20 ml) and water (15 ml) was added with gentle heating. After the solution was kept standing at room temperature overnight, water (20 ml) was added, followed by ultrasonication. After being collected by filtration, the solid was washed with water (30 ml, 20 ml), then washed with diisopropyl ether (20 ml), and dried under reduced pressure, to yield a solid (9.10 g). The solid obtained (9.00 g) was dissolved in acetone (30 ml), and after the solution was filtered, diisopropylether (50 ml) was added to the filtrate. A crystal seed was placed, and the mixture was kept standing at room temperature overnight. Precipitated crystals were collected by filtration, washed 3 times with diisopropyl ether (10 ml), and dried under reduced pressure, to yield crystals (7.85 g). The crystals obtained (7.80 g) were dissolved under heating in acetone (22.5 ml) and water (30 ml), and this solution was kept standing at room temperature for 1 hour. A precipitated solid was collected by filtration, washed with acetone-water (1:4) (15 ml), and dried under reduced pressure, to yield a solid (3.88 g). The solid obtained (3.88 g) was dissolved under heating in acetone (4 ml) and diisopropyl ether (14 ml) was added. This solution was kept standing at room temperature for 30 minutes. Precipitated crystals were collected by filtration, twice washed with diisopropyl ether (6 ml), and dried under reduced pressure, to yield crystals of R(+)-lansoprazole (3.40 g, optical purity 99.8%ee).

m.p.: 147.0–148.0° C. (dec.); Elemental analysis; Calculated: C: 52.03, H: 3.82, N: 11.38, S: 8.68, F: 15.43, O: 8.66; Found: C: 51.85, H: 3.92, N: 11.26, S: 8.82, F: 15.22; ¹H-NMR: 2.24 (3H, s), 4.38 (2H, q, J=7.8 Hz), 4.74 (1H, d, J=13.6 Hz), 4.87 (1H, d, J=13.6 Hz), 6.68 (1H, d, J=5.8 Hz), 7.26–7.36 (2H, m), 7.45(1H,m), 7.78 (1H, m), 8.35 (1H, d, J=5.8 Hz). IR(vcm⁻¹): 3083, 3034, 2975, 1586, 1478, 1441, 1306, 1267, 1163; UVmax(CHCl₃): 283.6 nm; [α]_D=+180.3° (c=1.004%, CHCl₃).

TABLE 2

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
7.560	0.141	11.6841	100
13.060	0.165	6.7733	44
15.160	0.141	5.8394	55
15.440	0.141	5.7342	84
20.040	0.165	4.4271	23
21.720	0.165	4.0883	89
22.560	0.141	3.9380	24
22.820	0.141	3.8937	24
24.080	0.165	3.6927	37

TABLE 2-continued

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
26.120	0.118	3.4088	32
28.680	0.165	3.1100	20

Example 3

Crystal of (R)-2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-Lansoprazole) 1.5 Hydrate

Amorphous (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole as obtained in Reference Example 1 (100 mg) was dissolved in ethanol (0.15 ml), and water (0.15 ml) was added. After a seed was placed, the solution was kept standing at room temperature for 1 hour. Precipitated crystals were collected by filtration, twice washed with water (2 ml), and dried under reduced pressure, to yield crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) 1.5 hydrate (96 mg). m.p. : 76.0–80.0° C.; Elemental analysis; Calculated: C: 48.48, H: 4.32, N: 10.60, S: 8.09, F: 14.38, O: 14.13; Found: C: 48.52, H: 4.44, N: 10.49.

TABLE 3

X-ray Powder Diffraction Data			
2θ (°)	Half-value width	d-value (Å)	Relative intensity (%)
6.680	0.165	13.2212	9
9.200	0.165	9.6046	21
9.960	0.141	8.8734	25
10.980	0.165	8.0513	42
13.380	0.141	6.6120	22
14.960	0.141	5.9170	63
15.680	0.165	5.6469	100
17.640	0.212	5.0237	34
19.760	0.212	4.4892	33
25.420	0.188	3.5010	23
29.800	0.188	2.9957	20

Experimental Example 1

Suppressive action on gastric mucosal injury due to stress of water immersion restraint in rat.

Male SD rats (7 weeks of age, weighing 230 to 250 g) were fasted for 24 hours, after which they were stressed by being housed in restraint cages and immersed to below the xiphoid process in a standing position in a 23° C. constant-temperature water chamber. After 5 hours, the rats were removed from the cages and sacrificed using gaseous carbon dioxide, and their stomachs excised. After the lower portion of the esophagus was clipped, a 1% formalin solution (10 ml) was injected into the stomach via the duodenum, which was then occluded, and the stomach was immersed in the same solution. After 10 minutes, an incision was made along the greater curvature, and the length (mm) of each mucosal injury was measured under a stereomicroscope. The overall sum of the injury lengths in each stomach was taken as the gastric mucosal injury index.

The crystals of (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (R(+)-lansoprazole) as obtained in Example 2 were suspended in 0.5% methyl cellulose (pH 9.5) containing 0.05 M NaHCO₃ and orally administered at 30

minutes before stressing (dosing volume 2 ml/kg). Each treatment group comprised 9 animals. The control group (solvent administration group) and the drug administration group were compared by Steel's test.

The results are shown in Table 4.

TABLE 4

Sample	Dose (mg/kg)	Gastric mucosal injury index (mm)	Suppression rate (%)
Control	—	10.9 ± 1.9	—
(R)-lansoprazole crystal	3	0.2 ± 0.2*	98.0

Each figure of gastric mucosal injury index is the mean ± standard error for the 9 animals in each group.
*p < 0.01 (versus control group, Steel's test)

Experimental Example 2

The crystals of R(+)-lansoprazole as obtained in Example 2 (about 5 mg) and amorphous R(+)-lansoprazole as obtained in Reference Example 1 (about 5 mg) were each taken in a colorless glass bottle, and their stability during storage at 60° C. (stopper removed) was examined. A 25 ml solution (concentration: about 0.2 mg/ml) of the sample after completion of storage in the mobile phase, along with a standard solution prepared using the initial lot, was analyzed under the HPLC conditions shown below, and the R(+)-lansoprazole content (residual percentage) was calculated from the peak area obtained. The results are shown in Table 5.

HPLC analytical conditions	UV 275 nm
Detection wavelength:	
Column:	YMC Pro C18, 4.6 × 150 mm
Mobile phase:	Fluid prepared by adding phosphoric acid to water/acetonitrile/triethyl amine (63:37:1) to reach pH 7.
Flow rate:	1.0 ml/min
Column temperature:	40° C.
Sample injection volume:	10 µl

TABLE 5

Stability of R(+)-Lansoprazole Crystal and Amorphous			
Sample	Duration of storage	Description	Content (Residual percentage)
Crystal	1 week	Light-brown	97.0
	2 weeks	Brown	93.8
	4 weeks	Brown	91.7
Amorphous	1 week	Brown	70.8
	2 weeks	Blackish brown	57.5

When the sample was stored at 60° C. (exposed), the crystal of Example 2 retained a content exceeding 90% for up to 4 weeks, whereas the amorphous form of Reference Example 1 showed reduction in content to 70.8% after 1 week and 57.5% after 2 weeks. This finding demonstrates

that the crystal of R(+)-lansoprazole is more stable and more preferable for use as a pharmaceutical etc. than the amorphous form.

INDUSTRIAL APPLICABILITY

The crystal of the present invention is useful as a pharmaceutical because it shows excellent antiulcer action, gastric acid secretion inhibiting action, mucosa-protecting action, anti-*Helicobacter pylori* action etc., and because it is of low toxicity. Furthermore, by crystallizing the (R)-isomer, not only its stability is improved but also its handling is facilitated so that it can be prepared as a solid pharmaceutical composition with good reproducibility. In addition, when orally administered, the crystal of the present invention is more absorbable and more rapidly shows its action than the racemate. In addition, when administered, the crystal of the present invention shows a higher Cmax and a greater AUC. than the racemate, and becomes less likely to be metabolized partly because of the increased protein-binding rate, thus showing an extended duration of action. The crystal of the present invention is therefore useful as a pharmaceutical of low dosage and with a low prevalence of adverse reactions.

What is claimed is:

1. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 11.68, 6.77, 5.84, 5.73, 4.43, 4.09, 3.94, 3.89, 3.69, 3.41 and 3.11 Angstrom.
2. A crystal of (R)-2-(((3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole 1.5 hydrate wherein the X-ray powder diffraction analysis pattern has characteristic peaks at interplanar spacings (d) of 13.22, 9.60, 8.87, 8.05, 6.61, 5.92, 5.65, 5.02, 4.49, 3.50 and 3.00 Angstrom.
3. A pharmaceutical composition which comprises the crystal according to claim 1 and a pharmaceutically acceptable excipient, carrier or diluent.
4. A pharmaceutical composition which comprises the crystal according to claim 2 and a pharmaceutically acceptable excipient, carrier or diluent.
5. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 1.
6. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 1 with a pharmaceutically acceptable excipient, carrier or diluent.
7. A method for manufacturing a pharmaceutical composition for treating or preventing digestive ulcer comprising formulating the composition with the crystal of claim 2.
8. A method for treating or preventing digestive ulcer in a mammal in need thereof which comprises administering to said mammal an effective amount of the crystal according to claim 2 with a pharmaceutically acceptable excipient, carrier or diluent.

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(57) **ABSTRACT**

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

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PHARMACEUTICAL FORMULATION AND PROCESS FOR ITS PREPARATION

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

OUTLINE OF THE INVENTION

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

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

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

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

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

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

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

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

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

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

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

"Test of Integrity of the Film":

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

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

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

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

"Release Test":

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

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

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

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

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

[0037] The invention thus relates to a multiparticulate tablet with improved gastro-protection, comprising at least one pharmaceutically active substance in the form of enteric coated particles, and a mixture of tableting excipients. The said mixture of excipients comprising xylitol or maltitol, each in a directly compressible form, a disintegrating agent, a lubricant and at least one other diluent. The ratio of a) the xylitol and/or the maltitol to b) the other diluent(s) is less than 5/95 (weight/weight), preferably less than or equal to 31/97 (weight/weight), more preferably still approximately 1/99 (weight/weight).

[0038] According to one aspect the pharmaceutically active substance is a proton pump inhibitor compound. Thus, according to this aspect the invention relates to a multiparticulate tablet with improved gastro-protection, comprising at least one proton pump inhibitor, such as omeprazole or esomeprazole, in the form of enteric coated particles, and a mixture of tableting excipients. The said mixture of excipients comprising xylitol or maltitol, each in a directly compressible form, a disintegrating agent, a lubricant and at least one other diluent. The ratio of a) the xylitol

and/or the maltitol to b) the other diluent(s) is less than 5/95 (weight/weight), preferably less than or equal to 3/97 (weight/weight), more preferably still approximately 1/99 (weight/weight).

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

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

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

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

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

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

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

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

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

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

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

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

[0050] drying.

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

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

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

[0054] drying.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[0094] The multiparticulate tablet is preferably an orodispersible tablet comprising a mixture of tableting excipients chosen from the group consisting of at least xylitol and/or maltitol, each in a directly compressible form, at least one disintegrating agent, at least one lubricant and at least one other diluent, the ratio of a) the xylitol and/or the maltitol to b) the other diluent(s) is less than 5/95 (weight/weight), and optionally, tableting excipients chosen from the group comprising swelling agents, antistatic agents, permeabilising agents, sweeteners, flavoring agents and colors.

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

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

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

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

[0098] Advantageously, the diluent is mannitol.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[0130] The examples below illustrate the invention.

Excipients Used

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

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

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

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

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

[0136] Aspartame: sold by Nutrasweet.

[0137] Potassium acesulfame: sold by Sunnett.

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

[0139] Magnesium stearate: sold by Peter Graven.

[0140] Citric acid: sold by Jungbunzlauer.

Equipment

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

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

Methods

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

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

[0145] Release test: type II paddle device, USP, 100 revolutions/minute, 300 ml 0.1N HCl medium (pH 1.2), then 1000 ml pH 6.8 buffer (by addition to the medium of 700 ml of Na₂HPO₄·2H₂O),

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

EXAMPLE 1

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

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

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

1) Mixtures

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

TABLE 1

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

*Coated pellets of (S)-omeprazole Mg

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

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

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

2) Tableting

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

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

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

TABLE 2

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

3) Conclusions

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

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

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

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

EXAMPLE 2

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

TABLE 3

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

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

TABLE 4

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

3) Conclusions

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14. (canceled)

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

16. (canceled)

17. (canceled)

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

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

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

a) preparing active particles comprising a pharmaceutically active substance;

b) applying an enteric coating on the active particles;

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

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

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

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

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

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

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