



No. 09-019210- -00003-0000

Fecha: 2010-07-16 16:59:34 Dep. 2020 DIR.NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 62

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

②

**SOLICITUD
PUBLICADA**

Número del expediente: 9-019210
Solicitante: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**
Apoderado: **EMILIO FERRERO**
Título de la nueva creación o denominación del signo: **SISTEMA DE
LIBERACION CONTROLADA Y METODO PARA FABRICARLO**
Gaceta: 615

③ **OPOSICIÓN PRESENTADA POR:**

SOLICITANTE	Nombre: GYNOPHARM S.A.S	IDENTIFICACIÓN
Dirección: Carrera 14 N° 94-44 Piso 7 Torre B		C.C. ☐ NIT ☒
Nacionalidad o Domicilio: COLOMBIA		C.E. ☐ Otro ☐
Lugar de Constitución: BARRANQUILLA		Cual
Teléfono: 2 36 84 95 Fax:		Número 802,006,279-4
E-mail:		
REPRESENTANTE O APODERADO	Nombre: CIELO ANGELA PEÑA RODRIGUEZ Dirección: CARRERA 13 No. 119-95 Teléfono: (571)213 12 13 Fax: (571)612 19 79 E-mail: negocios@optimum-co.com	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual Número 51.940.252 TP 82701

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art. 14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: **No cumple con los requisitos de patentabilidad**

Signo opositor:

Justificación:

**La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
revelado, ya se encontraba en el estado de la técnica. Es posible derivarlo de la
misma tal y como se demostrara en el capítulo "Fundamento de Hechos".**

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: CIELO ANGELA PEÑA RODRIGUEZ

FIRMA: 

C.C. 51.940.252

TP. 82701

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 09 019210

Asunto : Oposición a la solicitud de patente de Invención titulada
"SISTEMA DE LIBERACION CONTROLADA Y METODO
PARA FABRICARLO"

Solicitante : BOEHRINGER INGELHEIM INTERNATIONAL GMBH.

Opositora : GYNOPHARM S.A.S.

Publicada en la Gaceta de la Propiedad Industrial
N° 615 del 20 de abril de 2010

Yo, *CIELO ANGELA PEÑA RODRIGUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.S.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "SISTEMA DE LIBERACION CONTROLADA Y METODO PARA FABRICARLO", cuyos titulares son **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

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

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 25 de febrero de 2009 reivindicando prioridad bajo la solicitud EP20060017754 del 2006-08-25; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 615 del 20 de abril de 2010, cuya publicación internacional corresponde a la WO2008022932 del 2008-02-28.

2.2. La solicitud colombiana 09 019210 objeto de la presente oposición, está dirigida a proveer un sistema de liberación farmacéutica controlada, particularmente para administración oral, de sustancias activas con solubilidades dependientes del pH, que comprende un material de núcleo que comprende uno o más modificadores de pH farmacéuticamente aceptables; opcionalmente una capa aislante, una

primera capa que comprende uno o más polímeros insolubles en agua farmacéuticamente aceptables; una segunda capa que comprende por lo menos una sustancia activa como la flibanserina, que tiene una solubilidad dependiente del PH; una tercera capa que comprende uno o más polímeros farmacéuticamente aceptables que tienen grupos aniónicos o no iónicos; y opcionalmente una cuarta capa.

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

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



- D1: WO9819668 publicada el 14 de mayo de 1998.
- D2: US2005095293 publicada el 05 de mayo de 2005.

2.5. Ahora bien, el documento D1, se refiere a una formulación para la administración oral de sustancias activas con las características de solubilidad dependiente del pH y las sales farmacológicamente aceptables del mismo, lo que mejora la biodisponibilidad de la sustancia activa. El mismo documento D1, de forma particular en la página 3, en las líneas 15-29 de la página 5, en la figura 4, en los ejemplos y en el capítulo reivindicatorio describe un sistema de liberación de fármacos que comprende una pluralidad de pastillas, cada pastilla que comprende un núcleo de un material de base alcalina, múltiples capas de omeprazol separadas por barreras contra la humedad no entéricas (que incluye por ejemplo: etilcelulosa y HPMC), y una capa entérica que comprende polímeros que tienen grupos aniónicos.

2.6. El documento D2 por su parte se refiere a una composición farmacéutica para la administración oral de flibanserina, dicho documento D2 en el que de forma particular en los párrafos 002, en los ejemplos y en las reivindicaciones revela una composición farmacéutica para administración oral de flibanserina, que incluye "pellets" que poseen un núcleo que comprende un ácido orgánico, junto con un polímero soluble en agua, por ejemplo goma árabe, una capa aislante que comprende por ejemplo, goma árabe, una capa que contiene flibanserina y, por

ejemplo hidroxipropil celulosa, y un recubrimiento opcional, que incluye por ejemplo goma árabe.

2.7. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir del documento D2 por si solo o en combinación con D1, concebir un sistema de liberación farmacéutica controlada, particularmente para administración oral, de sustancias activas con solubilidades dependientes del pH, que comprende un material de núcleo que comprende uno o más modificadores de pH farmacéuticamente aceptables; opcionalmente una capa aislante, una primera capa que comprende uno o más polímeros insolubles en agua farmacéuticamente aceptables; una segunda capa que comprende por lo menos una sustancia activa como la flibanserina, que tiene una solubilidad dependiente del PH; una tercera capa que comprende uno o más polímeros farmacéuticamente aceptables que tienen grupos aniónicos o no iónicos; y opcionalmente una cuarta capa. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 019210 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con ninguno de los tres requisitos necesarios para su protección.

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

2.9.1. **CARENCIA DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización,*

comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”. A la fecha de prioridad, 25 de agosto de 2006 ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1 y D2, sistema de liberación farmacéutica controlada, particularmente para administración oral, de sustancias activas con solubilidades dependientes del pH, que comprende un material de núcleo que comprende uno o más modificadores de pH farmacéuticamente aceptables; opcionalmente una capa aislante, una primera capa que comprende uno o más polímeros insolubles en agua farmacéuticamente aceptables; una segunda capa que comprende por lo menos una sustancia activa como la flibanserina, que tiene una solubilidad dependiente del PH; una tercera capa que comprende uno o más polímeros farmacéuticamente aceptables que tienen grupos aniónicos o no iónicos; y opcionalmente una cuarta capa; sobre lo cual busca protección en el capítulo reivindicatorio.

- 2.9.2. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- “Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”. A la fecha de prioridad, 25 de agosto de 2006, a partir del documento D2 por sí solo, o en combinación con D1, un experto en la materia puede llegar de manera evidente a un sistema de liberación farmacéutica controlada, particularmente para administración oral, de sustancias activas con solubilidades dependientes del pH, que comprende un material de núcleo que comprende uno o más modificadores de pH farmacéuticamente aceptables; opcionalmente una capa aislante, una primera

capa que comprende uno o más polímeros insolubles en agua farmacéuticamente aceptables; una segunda capa que comprende por lo menos una sustancia activa como la flibanserina, que tiene una solubilidad dependiente del PH; una tercera capa que comprende uno o más polímeros farmacéuticamente aceptables que tienen grupos aniónicos o no iónicos; y opcionalmente una cuarta capa, sobre lo cual busca protección en el capítulo reivindicatorio.

2.9.3. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, en el capítulo reivindicatorio se reclaman usos y métodos terapéuticos y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo esto no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumple con el requisito de la aplicación industrial.

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

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada "SISTEMA DE LIBERACION CONTROLADA Y METODO PARA FABRICARLO", cuyos titulares son BOEHRINGER INGELHEIM INTERNATIONAL GMBH, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 615 del 20 de abril de 2010.

3. PRUEBAS

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

- D1: WO9819668 publicada el 14 de mayo de 1998.
- D2: US2005095293 publicada el 05 de mayo de 2005.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

5. ANEXOS

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

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO9819668 publicada el 14 de mayo de 1998.
 - D2: US2005095293 publicada el 05 de mayo de 2005.

6. NOTIFICACIONES

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

Señor Superintendente,



CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **CIELO ANGELA PEÑA RODRIGUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 82701 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **09 019.210**, titulada "**SISTEMA DE LIBERACIÓN CONTROLADA Y MÉTODO PARA FABRICARLO**", cuyo titular es **BOEHRINGER INGELHEIM INTERNATIONAL GMBH**, publicada en la gaceta No. 615 del 20 de abril de 2010.

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

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

Dado y Firmado en _____ (Colombia) a los ____ días del mes de ____ de 2010.

GYNOPHARM S.A.S.

Cédula de Extranjería: No. 319788.
Representante Legal

Acepto:


CIELO ANGELA PEÑA RODRIGUEZ
C.C. 51'940.252 de Bogotá
T.P.A. 82701 del C.S. de la J.



DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario del Circulo
de Bogotá, **US. ALBERTO**

DALAGOS ALACON
quien exhibió la C **E 349788**

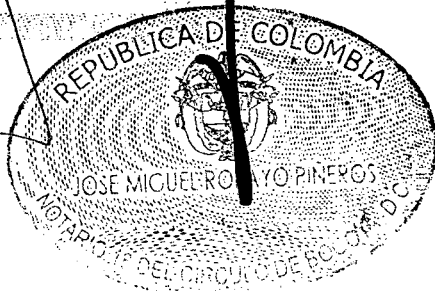
Expedida en **18A** y
declaró que la firma y huella que
aparecen en el presente documento
son suyas y que el contenido del mismo
es cierto. **02 JUL 2010**

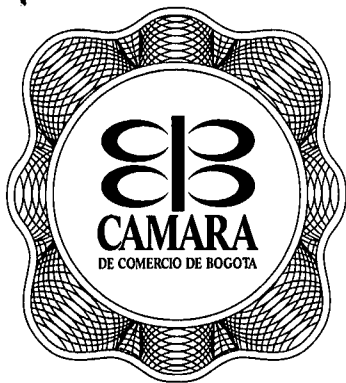
BOGOTÁ, D.C.

FIRMA

EL NOTARIO

HUELLA DEL
INDICE DERECHO





CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/07/09

HORA: 09:49:43

OPERACION: 09LJS0709062

PAGINA: 1

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

EL CONTENIDO DEL CERTIFICADO DE ESTA MATRICULA PUEDE VARIAR:
SE ENCUENTRA EN ESTUDIO UN DOCUMENTO

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

C E R T I F I C A

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM S.A. /-----

C E R T I F I C A

Que según Acta No. 22 del 29 de Abril de 2010 correspondiente a la Asamblea de Accionistas en Barranquilla, inscrito(as) en esta Cámara de Comercio, el 24 de Junio de 2010 bajo el No. 160,098 del libro respectivo, la sociedad antes mencionada-----se transformo en por acciones simplificada bajo la denominación de GYNOPHARM S.A.S.-----

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13
22	2010/04/29	Asamblea de Accionistas en Ba	160,098	2010/06/24

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.S.-----

SIGLA: .

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/07/09

HORA: 09:49:43

OPERACION: 09LJS0709062

PAGINA: 2

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

Correo

electrónico:

mvenegas@gynopharm.com.co

Pagina Web:

C E R T I F I C A

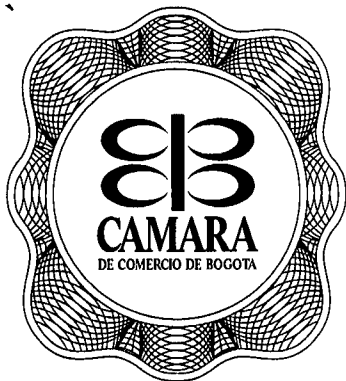
DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2087.

C E R T I F I C A

OBJETO SOCIAL: El objeto de la sociedad es el ejercicio de todas las actividades comerciales para: 1) La importacion, exportacion, fabricacion, comercializacion, distribucion y venta de productos farmaceuticos, higienicos, veterinarios e implementos medicos.

2) Cualquier otra actividad lícita de comercio relacionada con su objeto social principal y todo lo que se relaciona con la importacion de los bienes y equipos necesarios para el desarrollo de su objeto social. 3) Tener la representacion en Colombia de empresas o sociedades establecidas fuera del territorio colombiano, cuyo objeto sea similar o complementario. En desarrollo de su objeto social principal, la sociedad podra adelantar y celebrar los siguientes actos y contratos: A) Exportar e importar, agenciar, distribuir, comercializar, comprar o vender a comision o consignacion o de cualquier otra forma o modalidad, toda clase de equipos, aparatos, bienes al por mayor o al detal, y servicios relacionados con su actividad. B) Gravar en cualquier forma los bienes de su propiedad muebles o inmuebles, dar en prenda los primeros o hipotecar los segundos para garantizar obligaciones de la sociedad. C) Constituir apoderados que le representen, asociarse con otras compañías de la misma o parecida naturaleza y en general realizar toda clase de operaciones comerciales o civiles y ejecutar o celebrar toda clase de contratos o actos del mismo orden, ya sean industriales, comerciales o financieros encaminados a alcanzar los fines que se proponen. D) Adquirir, enajenar, administrar, recibir o

*** CONTINUA ***



*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/07/09

HORA: 09:49:43

OPERACION: 09LJS0709062

PAGINA: 4

debera obtener la autorizacion previa de la Junta Directiva. La sociedad tendra un Gerente quien sera elegido por Asamblea. El Gerente de la sociedad tiene a su cargo la administracion inmediata de la sociedad, asi como la representacion legal de la misma y en tal virtud le estan asignadas las siguientes funciones y atribuciones entre otras: Llevar la representacion de la entidad, tanto judicial como extrajudicialmente. Constituir, para casos especiales, apoderados judiciales o extrajudiciales. Celebrar los actos, operaciones y contratos conducentes al buen logro del objeto de la sociedad. Cualquier acto o contrato que supere en cuantia el equivalente a 300 SMLMV (TRESCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES) debera obtener la autorizacion previa de la Junta Directiva.-----

C E R T I F I C A

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.S.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

- | | |
|---|--------------------|
| 1. Llobet Poal Manuel | CC.*****14,670,196 |
| 2. Zanatta Reheman Leonardo Andres | CC.*****2,760,271 |
| 3. Munoz Marroquin Diego | CC.*****7,688,292 |
| 4. Montealegre Gonzalez Andres Leonardo | CC.*****79,950,262 |

Suplentes

- | | |
|-----------------------------------|--------------------|
| 1. Agudelo Pelaez Luis Hernando | CC.*****14,238,997 |
| 2. Aroca Almanza Arleth Ayelina | CC.*****36,718,415 |
| 3. Penaranda Urbina Adriana Paola | CC.*****53,120,683 |
| 4. tovar Vasquez Ruth | CC.*****52,175,756 |

C E R T I F I C A

Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.S. cuya parte pertinente se inscribió en esta Cámara de

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/07/09

HORA: 09:49:43

OPERACION: 09LJS0709062

PAGINA: 6

crito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

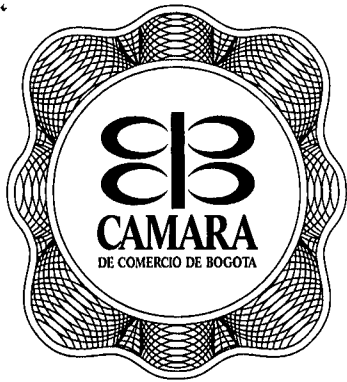
C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el senor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadania No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que por Escritura Pública No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria la. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,-----
consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora ----- CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadania numero 52.352.190, para que en nombre de la sociedad GYNOPHARM ----- S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ---- para: a) Recibir notificaciones de cualesquiera tipo de actos -----

*** CONTINUA ***



01



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17

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

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emanados de las autoridades administrativas o judiciales. b) -----
Presentar recursos por la via administrativa o judicial, renunciar
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administrativas y jurisdiccionales. d) Presentar demandas ante las
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Que en esta Cámara de Comercio no aparecen inscripciones posteriores
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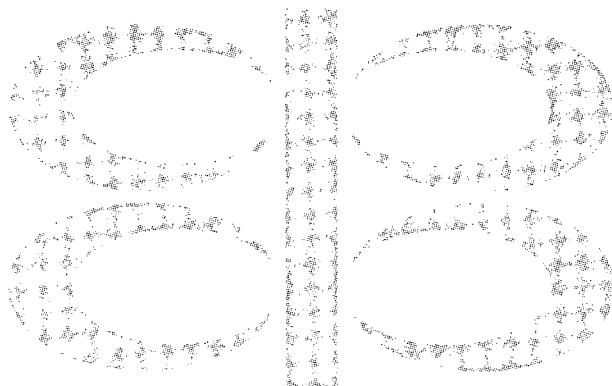
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Que su última Renovación fue el: 31 de Marzo de 2010.

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

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Que los actos de registro aquí certificados quedan en firme cinco
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18

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-019210- -00003-0000

Fecha: 2010-07-16 16:59:34 Dep. 2020 DIR.NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 62

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 58,533
FECHA : JULIO 16 DE 2010

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	327393393	09/07/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	356206723	09/07/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	356225833	09/07/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	356225844	09/07/2010	295,000.00
GYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	356225855	09/07/2010	295,000.00
...MAS INFORMACION NO IMP			TOTAL			2,065,000.00

***** CONCEPTO *****

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

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

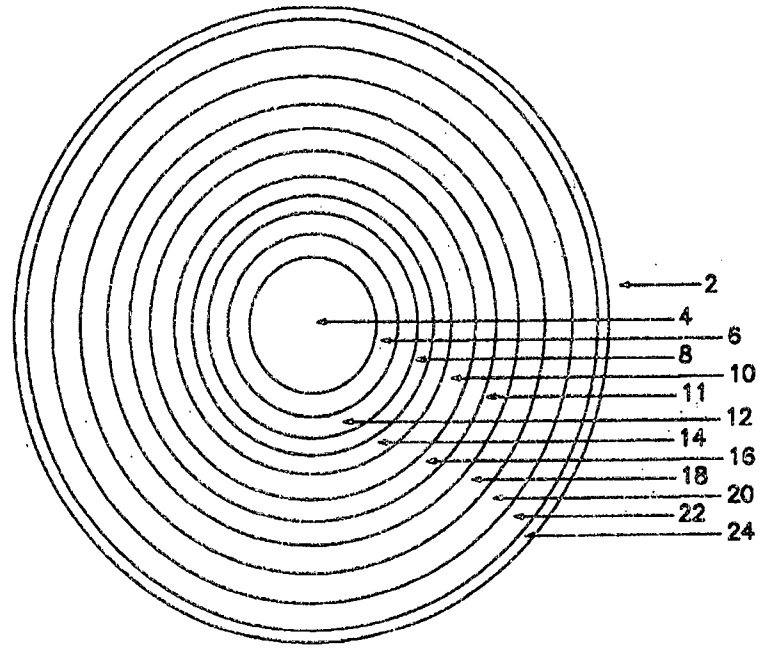
RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Anexo 1



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/50, 31/44		(11) International Publication Number: WO 98/19668
A1		(43) International Publication Date: 14 May 1998 (14.05.98)
(21) International Application Number: PCT/US97/20851 (22) International Filing Date: 5 November 1997 (05.11.97) (30) Priority Data: 08/740,981 6 November 1996 (06.11.96) US (71) Applicant (for all designated States except US): SHAR-MATEK, INC. [US/US]; 12 Walnut Drive, Long Valley, NJ 07853 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): SHARMA, Vinay, K. [US/US]; 12 Walnut Drive, Long Valley, NJ 07853 (US). (74) Agent: VIKSNINS, Ann, S.; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).		(81) Designated States: AU, ID, JP, KR, NO, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: DELAYED DELIVERY SYSTEM FOR ACID-SENSITIVE DRUGS		
		
(57) Abstract The present invention relates to a delayed release drug delivery system containing omeprazole capable of site-specific delivery and pulsatile (bolus) kinetics for once-a-day dosage comprised of an alkaline core structure sequentially layered with suspensions of omeprazole; a separation barrier; and an enteric barrier. The separation barrier is coated with a pH-dependent enteric membrane, which is relatively insoluble in gastric fluid but rapidly to immediately soluble in intestinal fluid, whereby the drug is released in a pulsatile manner in the proximal segment of the gastrointestinal tract.		

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DELAYED DELIVERY SYSTEM FOR ACID-SENSITIVE DRUGS

5

Background of the Invention

(1) Field of the Invention

The present invention relates to a drug delivery system and, more particularly, to a delayed release drug delivery system for drugs or biologically active materials (e.g., vitamins, vaccines, antibiotics, antifungal agents, muscle relaxers, mood altering drugs, and the like), and especially omeprazole. The system is capable of site-specific delivery and pulsatile (bolus) kinetics.

(2) Description of Prior Art

Omeprazole provides a powerful inhibitory action against secretion of gastric juices and can be used for treatment of gastric and duodenal ulcers. (*Lancet*, Nov. 27, 1982, pp. 1223-24). However, omeprazole is susceptible to degradation in acidic, acid reactive and neutral media, i.e., the half-life of degradation at pH 4 is less than six minutes, whereas at pH 7 it is about 14 hours. Human pharmacological studies have found that the rate of release of omeprazole can influence the total extent of absorption of the drug to the general circulation. A fully bioavailable dosage form should release the drug rapidly in the proximal part of the gastrointestinal tract.

U.S. Patent No. 4,786,505 discloses that the stability of conventional formulae of omeprazole is not satisfactory. The reference describes a dosage form including a core region containing omeprazole mixed with alkaline compounds or an alkaline salt of omeprazole mixed with an alkaline compound, or an alkaline omeprazole salt alone coated with one or more layers. The layer/layers which is/are comprised of an alkaline material separates/separate the core material from the outer layer, which is an enteric coating disposed on a subcoating. The final enteric-coated dosage form is treated to reduce water content in order to obtain stability of the drug during long-term storage.

U.S. Patent No. 4,853,230 describes a pharmaceutical preparation comprising an alkaline-reacting core containing an acid-labile pharmaceutical

substance and a pH-buffering alkaline-reacting compound which provides a pH of 7-12 to the micro-environment of the acid labile compound. A subcoating layer is composed of tablet excipients, film forming compounds, and alkaline buffering compounds. Finally, an enteric coating layer surrounds the subcoating layer, wherein the subcoating layer isolates the alkaline-reacting core from the enteric coating layer such that the stability of the product is enhanced.

Omeprazole, along with many other drugs (e.g., Captopril) or biologically active materials (e.g., beta-lactams), vitamins, vaccines, antibiotics, antifungal agents, muscle relaxers, mood altering drugs, and the like can be acid sensitive. That is, their active properties can decrease significantly in the presence of acids, usually by deterioration of the drug or chemical reaction with the drug, altering its composition. The use of enteric layers, which generally comprise layers with carboxyl groups or other acid groups, can adversely affect the stability of the acid sensitive ingredients, since the acid groups on the polymers or other ingredients used in the enteric coating can directly contribute to the acid sensitizing capability of the environment of the pellets during storage.

SUMMARY OF THE INVENTION

The present invention provides a delayed release drug delivery system containing an acid sensitive drug which is stable at pH levels above 9.0, or biologically active material which is acid sensitive yet stable at pH levels above 9.0, such as omeprazole, for once-a-day dosage. The present invention provides a dose of an acid sensitive drug which is stable at pH levels above 9.0, or biologically active material which is acid sensitive yet stable at pH levels above 9.0, such as omeprazole comprising an alkaline core structure of high cohesiveness and integrity, capable of withstanding the pressure of attrition during a layering operation. One aspect of the present invention is to take advantage of the alkaline core structure, for optimization of release and stability of acid sensitive drugs such as with omeprazole release. Another aspect of the present invention is to provide a delayed release dosage form of an acid sensitive drug, such as omeprazole which is resistant to dissolution in acid media. Another aspect of the invention is to provide at least one sub-separation layer in

the pellets adjacent to a layer containing the active acid sensitive material, the sub-separation layer comprising a water soluble/water dispersible polymer and a pharmaceutically acceptable water soluble buffer which can provide a pH of at least 9.0 (depending upon the stabilization needs of the individual compounds), preferably at least 9.5, more preferably at least 10.0, and most preferably (in the case of omeprazole), at least 10.5 or at least 11.0 (up to 12, for example). The use of the high pH buffer materials assures that even in the presence of moisture which could cause migration of acid within the pellets, the high pH buffer would reduce any effect that migratory acid could have on the system.

10 A further aspect of the present invention is to provide a delayed release dosage form of an acid sensitive drug such as omeprazole which dissolves rapidly in neutral-to-alkaline media. A still further aspect of the present invention is to provide a delayed release dosage form of omeprazole having good stability during long term storage.

15 The present invention includes both multicompartment pellets and monocompartment pellets for the release of acid sensitive drugs or biologically active materials. The monocompartment pellets, for example, might include a substrate (e.g., nonpareil), a subseparation layer (e.g., a water-soluble or water dispersible binder or polymer (especially cellulose based polymers), such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose incorporates and mixtures thereof (including with other types of water soluble or water insoluble polymers and binders, which two layers define an alkaline core structure) and a layer of deposited omeprazole, especially as from suspensions of omeprazole or micronized omeprazole, followed by a semipermeable moisture barrier layer, and finally with an enteric barrier layer. An optional finishing layer may also be provided. The preferred alkaline structure is comprised of a core of a blend of a spheronizing/disintegrating agent such as microcrystalline cellulose and an alkaline material such as magnesium trisilicate or trisodium phosphate, although buffers or salts having the pH range of properties described above may be used.

25 30 The alkaline core structure is of high integrity and can withstand pressure of attrition during rotor layering operation and subsequent application of an

aqueous suspension of omeprazole. The drug layered alkaline core structure is coated with a non-enteric moisture barrier, and then coated with a pH-dependent, enteric membrane, insoluble in simulated gastric fluid but dissolving immediately in intestinal fluid thereby releasing omeprazole by disintegration in the proximal segment of the gastrointestinal tract in a pulsatile manner.

BRIEF DESCRIPTION OF THE DRAWINGS

A better understanding of the present invention as well as other objects and advantages thereof will become apparent upon consideration of the detailed disclosure thereof, when taken with the accompanying drawings, wherein

Figure 1 is the dissolution profile of a delayed delivery system for omeprazole at pH 5.2;

Figure 2 is the dissolution profile of a delayed delivery system for omeprazole at pH 6.0; and

Figure 3 is the dissolution profile of a delayed delivery system for omeprazole at pH 7.2.

Figure 4 is a representation of a tablet dose unit within the scope of the present invention.

Figure 5 is the drug release profile for a Multi-Compartment enteric delayed release system of the present invention with the omeprazole, using trisodium phosphatate as the alkaline component.

DETAILED DESCRIPTION OF THE INVENTION

The delayed release drug delivery system of the present invention containing omeprazole is comprised of an alkaline core structure; layered omeprazole dispersion in aqueous dispersion of water soluble binder, such as hydroxypropylmethyl cellulose, other cellulose esters, water soluble polymers and the like; a separation barrier, which may be a non-enteric moisture barrier; and a delayed release enteric barrier providing gastro-resistant behavior to deliver omeprazole in the proximal segment (pH 5-6) of the gastrointestinal tract.

Microcrystalline cellulose is the preferred binder as it assists in the absorption of water, which is used to create an alkaline micro-environment for

each nonpareil central core by providing a hydroxyl ion concentration gradient. Once contact with water is made, there is migration of hydroxyl ions seeking a lower pH, moving toward omeprazole particles to enhance dissolution and to stabilize the omeprazole during dissolution in the acidic medium. A barrier of
5 low water-solubility polymer or resin, such as ethylcellulose, cellulose acetate, or zein is provided to protect omeprazole-layered particles from subsequent delayed release membrane coats containing carboxylic functionalities during the coating operation.

I. Alkaline Core Structure

10 Basic alkaline material is selected from the group consisting of salts of strong basic cations and weak acidic anions such as Mg^{2+} , Ca^{2+} , or Al^{3+} and CO_3^{2-} , OH^- , and metal oxides including MgO , CaO , and Al_2O_3 , at a preferred pH of 9 or greater; organic buffers including Tris (hydroxymethyl) amino methane; and natural clays including montmorillonite and pharmaceutical necessities including
15 sodium glycerophosphate (pH 9.5) and sodium borate (pH 9.5), ratio of omeprazole to alkaline material being from 1:1 to 1:5, preferably 1:1.5 – 1:2.5.

The alkaline core structure, in association with a spheronizing/disintegrating agent, is prepared by rotor layering nonpareils (e.g., 30/35 or 25/30 mesh, usually between 20 and 50 mesh) with a powder blend of
20 water softenable polymer such as microcrystalline cellulose and an alkaline agent such as trisodium phosphate or magnesium trisilicate powder. A dispersion of hydroxypropyl cellulose is preferably used as a polymeric binding agent for depositing powder blend on the nonpareils. The powder blend and the binding agent are applied at appropriate powder feed rate, spray rate, air volume,
25 and inlet temperature. Ratio of spheronizing/disintegrating agent is from 2:1 to 1:2, preferably 1:1.5 to 1.5:1.

II. Layered Drug Deposit

The layered omeprazole macroparticulates may be obtained by layering micronized omeprazole dispersion in an aqueous dispersion of water
30 soluble/dispersible organic polymeric binders, especially cellulose-based polymers such as hydroxypropyl methylcellulose (traded as Opadry™

Y-5-7095, a registered trademark of Colorcon) or polysiloxane polymers such as Simethicone Emulsion 30% USP on the alkaline deposit cores using rotor layering equipment.

III. Separation Barrier

5 The separation barrier is then created over the layered drug deposit. After the drug layering operation, the layer may be formed by any commercial process, such as for example, layering over the drug layer a dispersion of trisodium phosphate and Opadry White YS 22-7719, or a semipermeable barrier composed of water soluble or water dispersible polymers (such as cellulose-
10 based polymers, such as cellulose esters, acetates, other derivatives and copolymers), ethylcellulose (e.g., Surelease®, Colorcon), cellulose acetate or zein.

Application of trisodium phosphate (or other pharmaceutically acceptable buffer with a pH greater than 9.0, etc. (as described below) as a separation
15 barrier may be accomplished by any commercially available process such as suspension layering, powder layering, or compression molding the trisodium phosphate (or other buffer) with a water-soluble binder (e.g., lactose or other pharmaceutically acceptable binder, including other sugars or carbohydrates), preferably when both materials are micronized, or dissolving the buffer, e.g., the
20 trisodium phosphate with a cosolvent (e.g., Carbowax®3350 or 8000).

The barrier thus created inhibits the interaction between dissolved omeprazole (or other acid sensitive drug or biologically active material) and carboxylate ions provided by the delayed release pH enteric barrier. Inhibition of such interaction provides protection to omeprazole from degradation and
25 discoloration.

IV. Delayed Release Enteric Barrier

The delayed release enteric barrier is applied on the non-enteric barrier-coated material by any convenient commercial coating or layering process such as rotor-layering or fluidized bed coating, using an aqueous dispersion of
30 the enteric coating composition, such as, for example, 30% w/w of copolymers of methacrylic acid and ethyl acrylate, plasticized with a nontoxic,

pharmaceutically acceptable plasticizer, such as organic plasticizers, and especially triethyl citrate. An antiadherent, such as talc, is used to prevent agglomeration of the membrane-coated beads. As enteric coating materials, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP-50), polyvinyl acetate phthalate (PVAP), co-polymerized acrylic polymers such as acrylic acid or methacrylic acid/methacrylic acid methyl esters (L30D-55), or similar compounds may be used, preferably HPMCP-50 and L30D-55.

The enteric coating layer also contains pharmaceutically acceptable plasticizers, such as water-soluble triacetin, triethyl citrate, or propylene glycol. The ratio of polymer to plasticizer may be, for example, between 10:1 to 6:1, preferably being 9:1 to 7:3, and more preferably 8.5:2 to 7.5:2; enteric polymers as selected, based on minimal lag time, followed by pulsatile kinetics; and minimal reactive carboxyl groups. Therefore, the organic-based enteric polymer, HPMCP-50 and water-based enteric polymer, L30D-55, are preferred, with an apparent pKa close to 4.3 (e.g., between 4.1 and 4.5). Insofar as the reactivity of carboxyl groups is concerned, all of these enteric materials produce degradation compounds which impart a tint of purple to the omeprazole-layered alkaline core structure. Therefore, in the present invention, a semipermeable barrier is intentionally applied between the omeprazole layer and the enteric membrane, in order to prevent the degradation of omeprazole.

V. Dissolution Profiles

Figure 1 represents the dissolution profile of a delayed delivery system for omeprazole at pH 5.2, and distinguishes between enteric membranes with regard to lag time and kinetics of drug release. As is evident from Figure 1, only CAT (cellulose acetate trimellitate) provides an acceptable, pulsatile release kinetics. However, CAT is not acceptable in this instance. Whereas pH 5.2 is acceptable for the fasted, but not for the non-fasted state, CAT would deliver the drug in the non-fasted stomach where the pH can approach 4-5 in some cases.

Figure 2 represents the dissolution profile of a delayed delivery system for omeprazole at pH 6.0, representative of the non-fasted state in the proximal segment of the small intestine. As indicated, HPMCP and L30D-55 provide an optimum pulsatile release profile at pH 6.0. CAT, on the other hand, while
5 providing an optimum pulsatile release profile at pH 6.0, is not acceptable; because of its low pKa, CAT would deliver the drug in the non-fasted stomach. The other materials, CAP and CAS, do not exhibit satisfactory pulsatile release profiles and, in fact, the profiles tend to become sigmoidal in shape.

Figure 3 represents the dissolution profile of a delayed delivery system
10 for omeprazole at pH 7.2. As shown, all enteric barrier materials provide acceptable pulsatile release kinetics; however, a pH of 7.2 approaches that of the large intestine, which is 7.5 to 8.0. Material having a higher pH, 7.2, will not deliver the drug in the proximal segment of the small intestine, where the pH ranges from 4.7 to 6.5. HPMCP and L30D-55 provide most appropriate
15 materials for optimum pulsatile release in the targeted area.

Figure 4 shows one example of a multicompartment, enteric delayed release system dose unit of the present invention 2 comprising a substrate 4 having alternating subseparation layers 6, 8, 10 and 11, and drug layers 12, 14, 16 and 18. A separation layer 20 overlays all of the previous layers and is in turn
20 covered with an enteric membrane 22 and a finish coat 24.

Figure 5 shows a drug release profile of a multicompartment, enteric delayed release system like that of Figure 4. As can be seen from the graph, the initial release of the omeprazole was delayed for approximately two hours, with a rapid and steady release occurring quickly over an approximately ten minute
25 period.

EXAMPLES

The specific nature of the composition of the present invention will be more fully apparent from consideration of the following specific examples of preferred embodiments thereof. In the examples, as in the preceding description,
30 all parts and percentages are given by weight unless otherwise indicated.

Example 1Preparation of Alkaline Core Structure

	Nonpareils 30/35 mesh	750 g.
	Magnesium Trisilicate	1500 g.
5	Microcrystalline Cellulose	1500 g.
	Klucel (6% w/w/ = 4175)	250.5g.

Total: 4000.5g.

- 10 The preparation of the alkaline core is achieved by using a blend of a
spheronizing agent such as microcrystalline cellulose and an alkaline material
such as magnesium trisilicate (preferably, in a 50/50 ratio) which is powder-
layered on 30/35 mesh non-pareils, using a 12" insert in a fluid bed granulator
dryer (traded as FLM-15 EX by Vector, Corporation, Marion, Ia.). Particle size
15 analysis is as follows:

Mesh	14	16	18	20	25	30	Pan
Percent Retained	2	22	64	10	1	1	4

- 20 The process yield was 90%. The theoretical potency of magnesium trisilicate is
375%.

Example 2Composition of Suspension for Layered Drug Deposit

25	Omeprazole	111 g.
	Opadry Y-5-7095	44.4g.
	Water, deionized	954.6g.
	Total:	1110g.

30

Example 3

Composition of Layered Drug Deposit

		<u>Solids, g.</u>	<u>%, w/w</u>
	Omeprazole	111	9.607
	Opadry Y-5-7095	44.4	3.843
5	Alkaline Core Structure	1000.0	86.550
		1155.4	100.000

10 The omeprazole layer dispersion is prepared by weighing purified water into a tared container equipped with a Lightnin Mixer with impeller. With vigorous mixing, hydroxypropyl methylcellulose (Opadry Y-5-7095) is dispersed in water to prepare a smooth paste. Then, remaining water is added to prepare a clear dispersion. To this dispersion, omeprazole (111 g.) is added, to obtain a final omeprazole concentration of 10% w/w. The omeprazole suspension is

15 suspension-layered on magnesium trisilicate pellets, using a 12" rotor insert in a fluid bed granulator dryer (traded as FLM-15 EX by Vector Corporation, Inc.).

Example 4

Preparation of Non-Enteric Moisture Barrier

20 To the drug deposit core, a 3% weight gain is applied, using a water-based dispersion of ethylcellulose (traded as Surelease[®] by Colorcon, Inc., Pa.). this is accomplished by using a 12" rotor insert in the FLM-15 EX fluid bed granulator dryer.

Example 5

Delayed Release Enteric Barrier(s)

	Eudragit L30D-55	594.3 g.
	Talc, U.S.P.	35.66 g.
5	Triethyl Citrate	35.66 g.
	Water, Deionized	334.33 g.
	Total:	1,000.00 g.

10 A water-based dispersion of Eudragit L30D-55, plasticized with triethyl citrate is applied to provide a weight gain of 15%. An antiadherent talc is used to prevent agglomeration of the membrane-coated beads.

	Cellulose Acetate Phthalate	100 g.
15	Diethyl Phthalate	25.08 g.
	Water, Deionized	26.25 g.
	Acetone, N.F.	848.75 g.
	Total:	1000.00 g.

20 An organic-based dispersion of cellulose acetate phthalate, plasticized with diethyl phthalate, is applied to provide a weight gain of 15%

	Cellulose acetate trimellitate, N.F.	100.08 g.
	Triacetin	25.08 g.
25	Water, Deionized	26.25 g.
	Acetone, N.F.	848.75 g.
	Total:	1000.00 g

30 An organic-based dispersion of cellulose acetate trimellitate, plasticized with triacetin, is applied to provide a weight gain of 15%.

12

	Hydroxypropyl methylcellulose phthalate (HPMCP-50)	100.0 g.
5	Acetylated monoglyceride (Myvacet 9-45)	15.0 g.
	Water, Deionized	44.25 g.
10	Acetone, N.F.	840.75 g.
		1000.00 g.

15 An organic-based dispersion of HPMCP-50, plasticized with Myvacet 9-45, is applied to provide a weight gain of 15%. A supercoat of 2% weight gain, using Poadry 7065 (10% w/w dispersion) is used to finish off the coating operation. The potency of omeprazole in imeprazole beads will be as follows:

20

Example 6

Potencies at Various Stages Coating. Percent

	Drug layered drug deposit	= 9.607
	Sub-coated drug layered beads (2% weight gain based on alkaline core structure)	= 9.444
25		
	Semipermeable barrier coat (1% weight gain)	= 9.364
30	Enteric-coated drug layered beads (15% weight gain)	= 8.312

Super-coated Enteric-coated
drug-layered beads
(2% weight gain) = 8.189

5 For 20 mg. dosage, therefore, 244 mg. of pellets are required.

Example 7

Composition of alkaline core structure

	Nonpareils 25/30 mesh	750.0 g
10	Trisodium Phosphate (1.5% w/w)	31.68 g
	Opadry White YS-22-7719 (16.39% w/w)	21.32 g
	TOTAL:	803.00 g

The preparation of the separation layer is achieved by suspension layering on
15 25/30 mesh nonpareil seeds a dispersion of trisodium phosphate and Opadry
White YS-22-7719 in purified water, using a twelve inch insert in a fluidized bed
granulator dryer (FLM-15-ES by Vector Corp., Marion, Ia). The total quantity
to be applied for five separation layers is 1289.4 grams.

20 Example 8

Composition of drug layer

	Omeprazole USP, micronized	165.0 g
	Lactose monohydrate fine powder	562.9 g
	Talc, USP	29.6 g

25 The powdered drug layer consists of 165.0 grams of micronized Omeprazole
USP and 592.5 grams Lactose monohydrate fine powder (micronized) and 29.6
grams of talc. The particle size of omeprazole and the excipients is below 20
microns. The theoretical quantity to be applied to the multilayered separation
30 layered pellets is 757.5 grams.

Example 9

Theoretical quantity to be applied to the individual separation and rug layers as a total weight of a batch preparation.

	Sublayer 1 To substrate	214.9 g
5	Drug layer 1 To separation layered pellets	189.4 g
	Sublayer 2 To drug layered pellets	214.9 g
	Drug layer 2 to separation layered pellets	189.4 g
	Sublayer 3 to drug layered pellets	214.9 g
	Drug layer 3 To separation layered pellet	189.4
10	Sublayer 4 to drug layered pellets	214.9 g
	Drug layer 4 To separation layered pellet	189.4
	Sublayer 5 to drug layered pellets	429.8 g

The total theoretical to be applied to the five separation layers and the four drug layers comprises 1289.4 grams and 757.6 grams, respectively.

Example 10

Composition of alkaline core structure

	Nonpareils 25/30 mesh	750.0 g
20	Trisodium Phosphate (1.06% w/w)	5.28 g
	Opadry White YS-22-7719 (16.38% w/w)	35.22 g
	TOTAL:	790.5 g

The preparation of the separation layer is achieved by suspension layering on 25/30 mesh nonpareil seeds a dispersion of trisodium phosphate and Opadry White YS-22-7719 in purified water, using a twelve inch insert in a fluidized bed granulator dryer (FLM-15-ES by Vector Corp., Marion, Ia). The total quantity to be applied for the alkaline core structure is 214.9 grams.

Example 11

Composition of drug layer

	Omeprazole USP,	135.35 g
	Opadry Y-5-7095	133.35 g
5	Simethicone Emulsion 30%, USP	0.606 g
	Total	267.306 g

The suspension of the layered drug deposit is composed of micronized drug particles in a dispersion of Simethicone emulsion 30% USP and Opadry White Y-5-7095 in purified water. Total theoretical quantity to be applied to the four
10 drug layers is 1333.5 grams. The Omeprazole suspension is suspension layered on the alkaline core structure (composed of water-soluble trisodium phosphate), using a twelve inch rotor insert in a fluid bed granulation dryer (FLM-15 ES, Vector Corporation, Marion, Ia).

15

While the invention has been described in connection with an exemplary embodiment thereof, it will be understood that many modifications will be apparent to those of ordinary skill in the art, and that this application is intended to cover any adaptations of variations thereof. Therefore, it is manifestly
20 intended that this invention be only limited by the claims and the equivalents thereof.

WHAT IS CLAIMED IS:

1. A drug delivery system for which comprises a plurality of pellets, each of said pellets comprising a core of a basic alkaline material, a coating of
5 omeprazole surrounding said core of alkaline material; and an enteric membrane, said system being characterized by having multiple layers of omeprazole separated by non-enteric moisture barriers surrounding omeprazole layers and at least one enteric layer comprising enteric film former plasticized with a water soluble plasticizer, said enteric membranes
10 having a weight gain sufficient to permit release of omeprazole after immersion in both 0.1N HCl for two hours for enteric behavior, followed by pH 6.8 buffer, said release corresponding to a drug release pattern of 0% of the total omeprazole released after at least 1.5 hours of measurement in 0.1N HCl and from 60-80% of the total omeprazole released after 45 minutes of measurement
15 in said pH 6.8 buffer.
2. The drug release system of claim 1 wherein said core comprises both a basic alkaline material and a spheronizing structuring agent.
- 20 3. The drug release system of claims 1 and 2 wherein each of said pellets comprise said core and at least three distinct drug layers comprising omeprazole, each of said drug layers being separated from other drug layers by sub-separation layers comprising moisture barrier layers.
- 25 4. The drug release system of claims 1 and 2 wherein each of said pellets comprise said core and at least three distinct drug layers comprising omeprazole, each of said drug layers being separated from other drug layers by sub-separation layers comprising moisture barrier layers, and wherein said moisture barrier layers comprise non-enteric moisture barrier comprising water-insoluble
30 semipermeable polymeric membranes.

5. The drug release system of claim 4 wherein said non-enteric moisture barrier layer comprises a cellulose-based resin.
6. The drug release system of claim 3 wherein said at least one enteric layer
- 5 comprising enteric film former plasticized with a water soluble plasticizer comprises a cellulose-based polymer.
7. The drug release system of claim 3 wherein said enteric coating comprises an acrylic resin.
- 10
8. The drug release system of claims 1 and 2 wherein each of said pellets comprise said core and at least three distinct drug layers comprising omeprazole, each of said drug layers being separated from other drug layers by sub-separation layers comprising moisture barrier layers, wherein said at least one enteric layer
- 15 comprising enteric film former plasticized with a water soluble plasticizer comprises a cellulose-based polymer or acrylic resin, and said water-soluble plasticizer comprises a plasticizer selected from the group consisting of triacetin, triethyl citrate and propylene glycol..
- 20 9. A delayed release drug delivery system of omeprazole for site-specific delivery and pulsatile (bolus) kinetics, which comprises a plurality of pellets, each of said pellets having a core of a basic alkaline material and a spheronizing structuring agent; a multi-layer coating of
- 25 a) at least one omeprazole layer surrounding said core of alkaline material;
- b) a non-enteric moisture barrier surrounding said at least one omeprazole layer; and
- c) at least one layer of an enteric membrane comprising enteric film former plasticized with a water soluble plasticizer,
- 30 said enteric membrane having a weight gain sufficient to permit release of omeprazole in 0.1N HCl for at least 1.5 hours for enteric behavior, followed by pH 6.8 buffer, corresponding to a drug release pattern of 0%

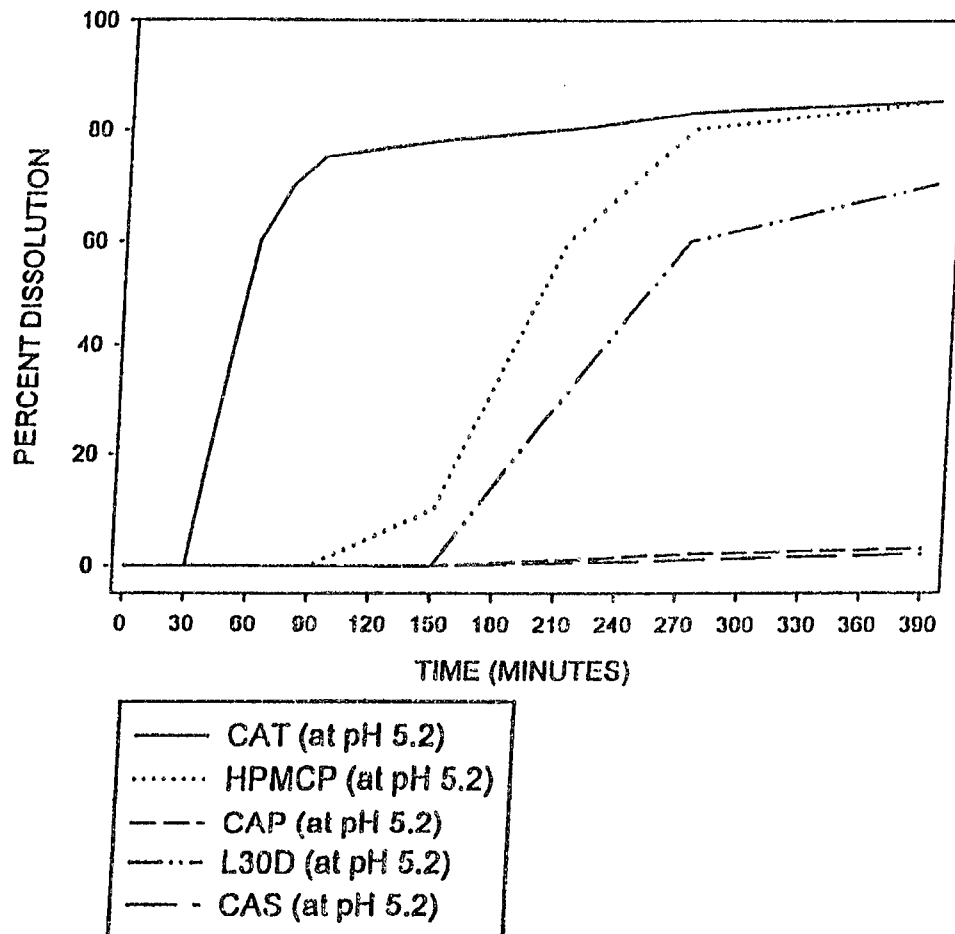
of the total omeprazole released after two hours of measurement in 0.1N HCl and from 60-80% of the total omeprazole released after 45 minutes of measurement in said pH 6.8 buffer.

- 5 10. The delayed release drug delivery system as defined in Claim 9, wherein said basic alkaline material is selected from the group consisting of salts of strong basic cations and weak acidic anions; organic buffers, natural clays, and sodium borate, the ratio of omeprazole to alkaline material being from 1:1 to 1:5.
- 10 11. The delayed release drug delivery system as defined in Claim 9, wherein said non-enteric moisture barrier is selected from the group consisting of water-insoluble, semipermeable polymeric membranes of ethylcellulose, cellulose acetate, and zein, wherein said delayed release enteric barrier is selected from the group consisting of acrylic and resin lacquers and being anionic polymers of
- 15 methacrylic acid, methacrylic acid esters or cellulose phthalic acid ester derivatives, wherein said plasticizer is selected from the group consisting of water-soluble triethyl citrate, triacetin, and propylene glycol, ratio of polymer to plasticizer being 9:1 to 7:3, and wherein the ratio of alkaline material to spheronizing/disintegrating agent is 2:1 to 1:2 in said central alkaline core
- 20 structure.
12. The delayed release pellets of omeprazole which comprises a plurality of pellets, each of said pellets having a core of a basic alkaline material and a spheronizing structuring agent; a multi-layer coating of omeprazole surrounding
- 25 said core of alkaline material; a non-enteric moisture barrier surrounding said omeprazole layers; and multilayers of an enteric membrane comprising enteric film form plasticized with a water soluble plasticizer, weight gain of said enteric membranes being sufficient to permit release of omeprazole in 0.1N HCl for two hours for enteric behavior, followed by pH 6.8 buffer, corresponding to a drug
- 30 release pattern of 0% of the total omeprazole released after two hours of

measurement in 0.1N HCl and from 60-80% of the total omeprazole released after 45 minutes of measurement in said pH 6.8 buffer.

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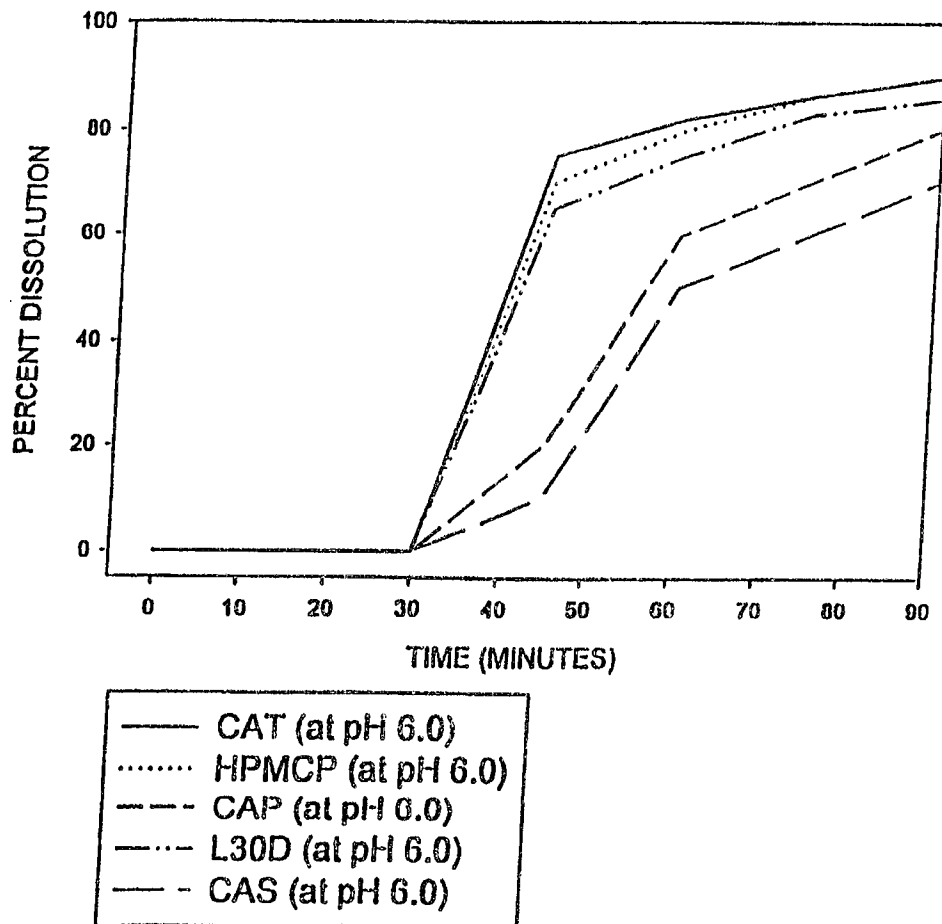
FIG. 1 DISSOLUTION PROFILE OF DELAYED DELIVERY SYSTEM
FOR OMEPRAZOLE AT pH 5.2
(With 30 Minutes Gastric Presoak)



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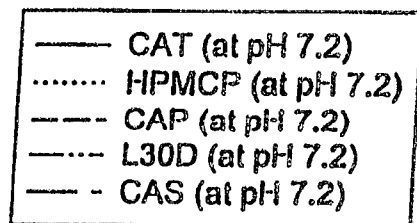
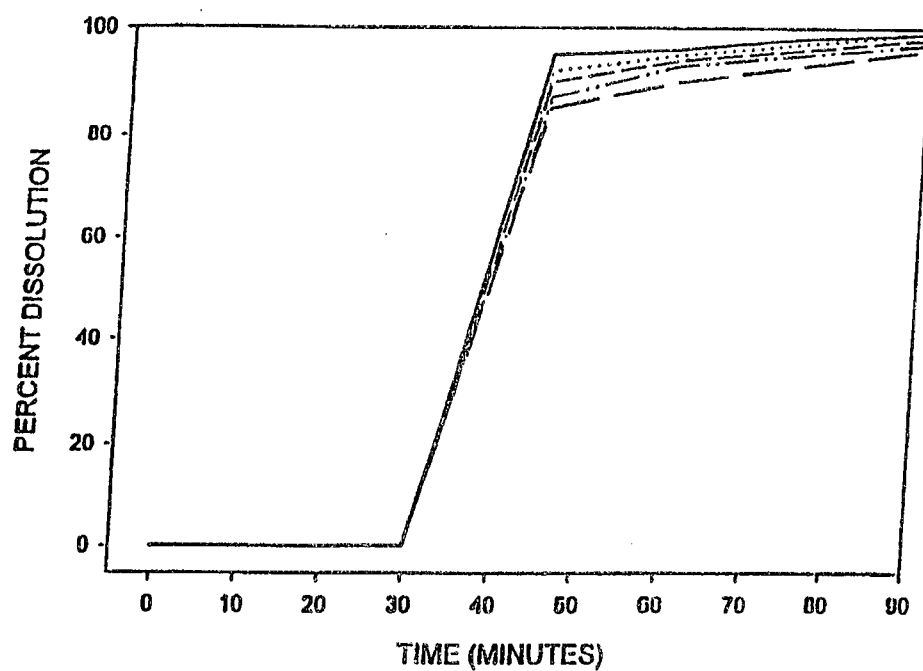
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FIG. 2 DISSOLUTION PROFILE OF DELAYED DELIVERY SYSTEM
FOR OMEPRAZOLE AT pH 6.0
(With 30 Minutes Gastric Presoak)



3/5

FIG. 3 DISSOLUTION PROFILE OF DELATED DELIVERY SYSTEM
FOR OMEPRAZOLE AT pH 7.2
(With 30 Minutes Gastric Presoak)



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4/5

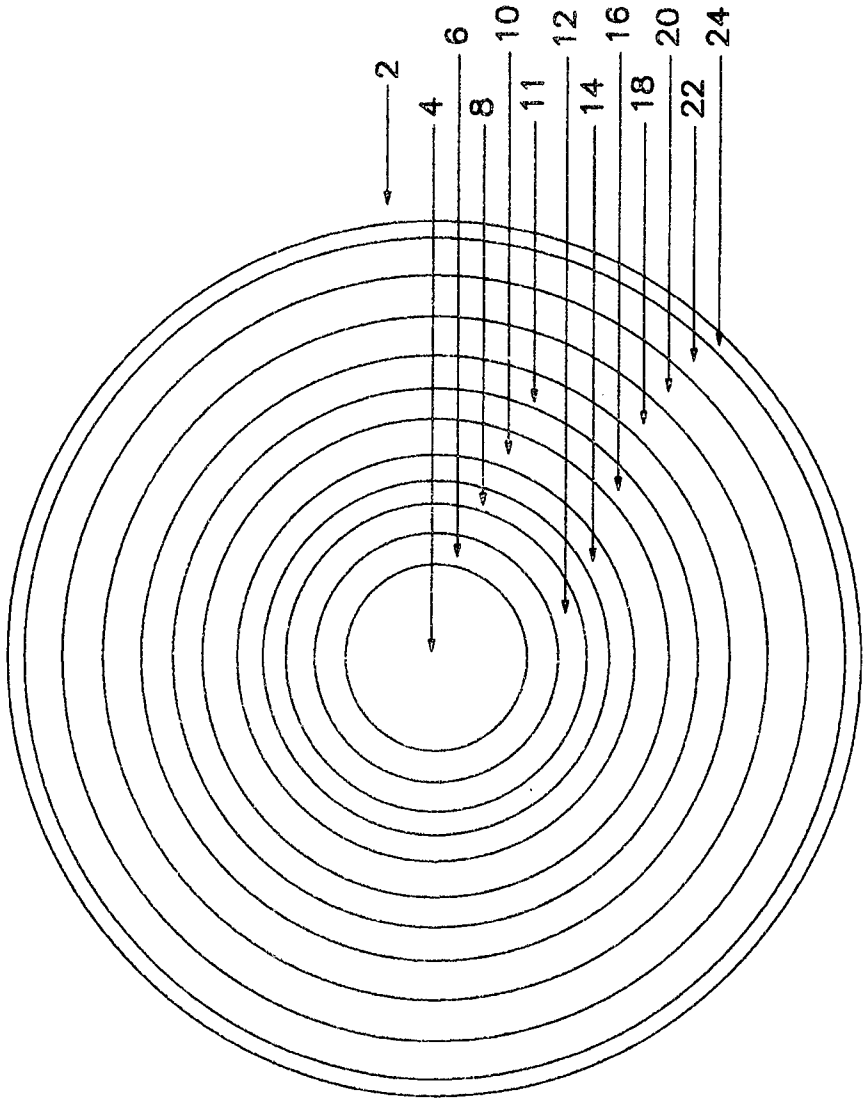


FIG. 4

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DRUG RELEASE PROFILE
Multi-Compartment Enteric Delayed Release System
(Suspension Layering)

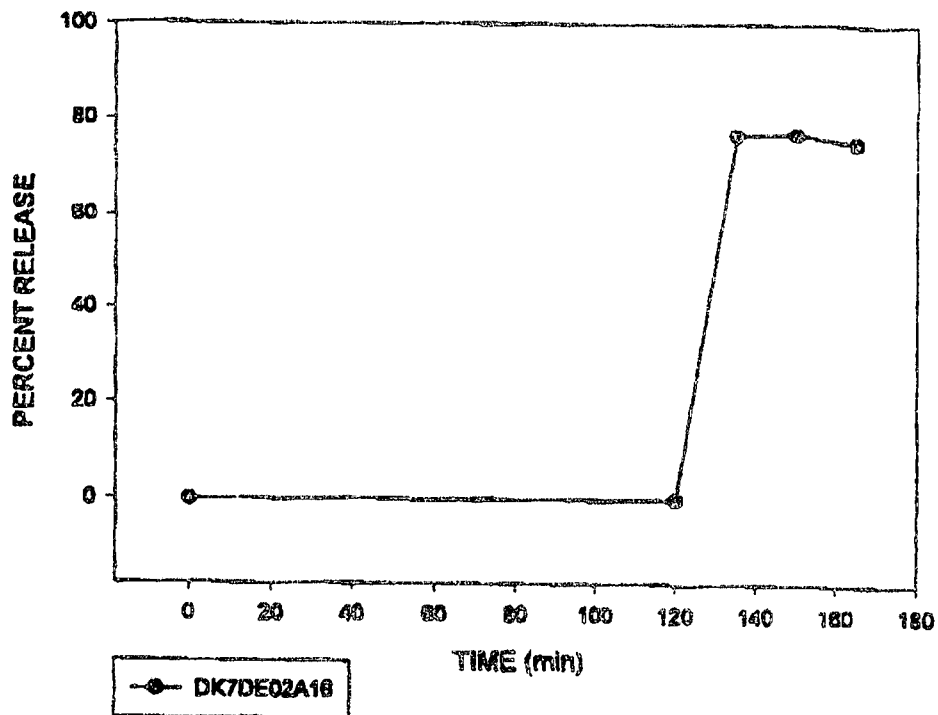


FIGURE 5

ANEXO 2



US 20050095293A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0095293 A1**
Brauns et al. (43) **Pub. Date: May 5, 2005**(54) **ADMINISTRATION FORM FOR THE ORAL
APPLICATION OF POORLY SOLUBLE
DRUGS**(22) **Filed: Sep. 3, 2004**(30) **Foreign Application Priority Data**(75) **Inventors: Ulrich Brauns, Biberach (DE);
Rolf-Stefan Brickl, Warthausen (DE)****Mar. 7, 2002 (DE)..... DE 102 09 982.0****Publication Classification****Correspondence Address:****MICHAEL P. MORRIS
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RIDGEFIELD, CT 06877-0368 (US)**(51) **Int. Cl.⁷ A61K 31/275; A61K 9/26**(52) **U.S. Cl. 424/469**(57) **ABSTRACT**(73) **Assignee: Boehringer Ingelheim Pharma GmbH
Co. KG, Ingelheim (DE)**

The invention relates to a new formulation for oral administration of active substances with pH-dependent solubility characteristics and the pharmacologically acceptable salts thereof, which improves the bioavailability of the active substance.

(21) **Appl. No.: 10/934,140**

Figure 1:

Diagrammatic structure of the pharmaceutical composition:

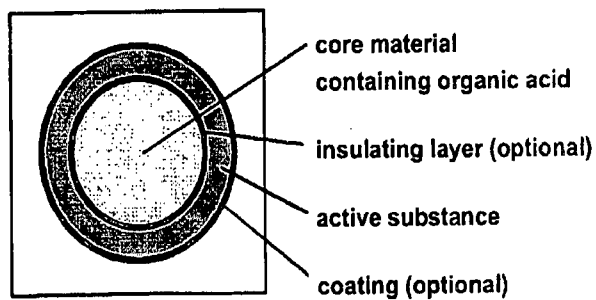


Figure 2:

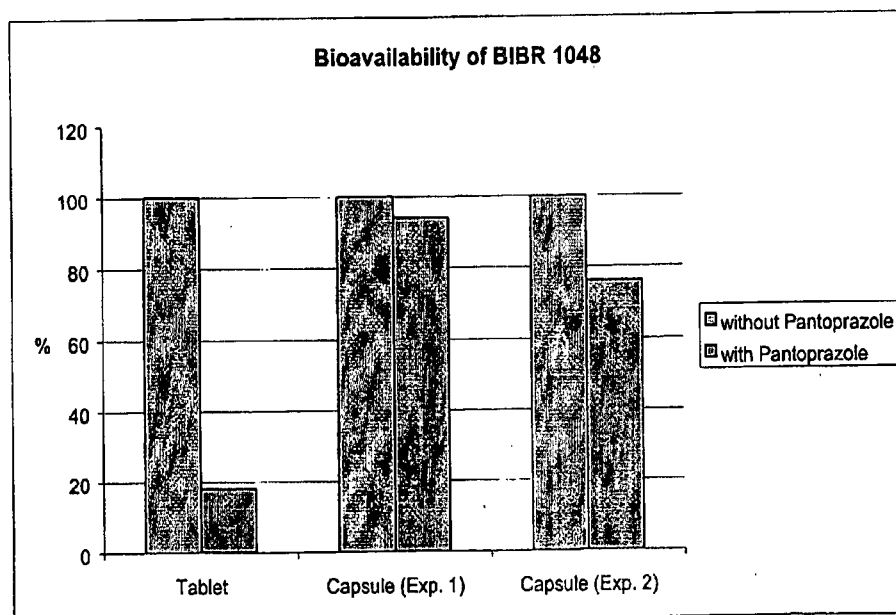
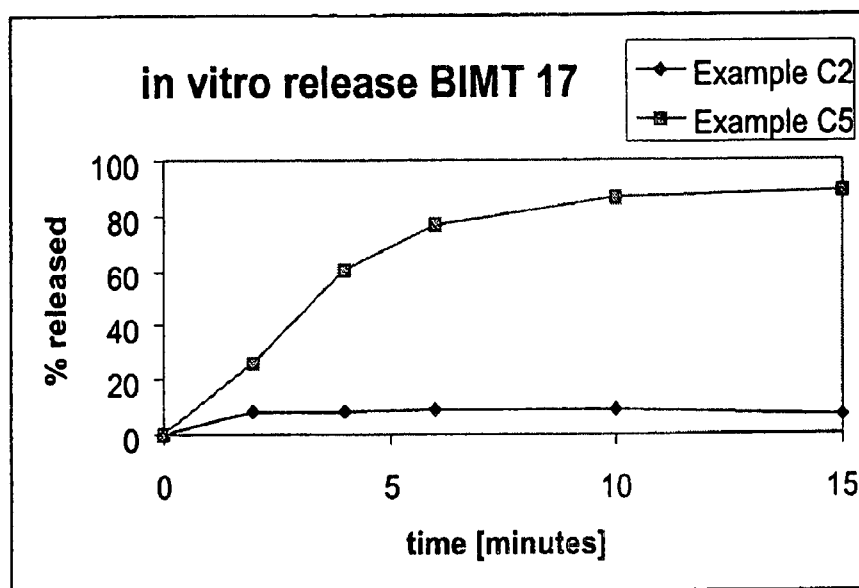


Figure 3:



ADMINISTRATION FORM FOR THE ORAL APPLICATION OF POORLY SOLUBLE DRUGS

FIELD OF THE INVENTION

[0001] The invention relates to a formulation for the oral administration of basic active substances with pH-dependent solubility characteristics, and the salts thereof.

DESCRIPTION OF THE FIGURES

[0002] FIG. 1 shows the schematic structure of a pharmaceutical composition according to the invention in the form of a sectional view of a pellet.

[0003] FIG. 2 graphically shows the bioavailability of the formulations according to the invention compared with the conventional tablet with and without the addition of pantoprazole.

[0004] FIG. 3 shows the in vitro releases of an Example C5 according to the invention compared with the reference formulation C2 with a similar active substance content in 0.005 mol citrate buffer pH 5.0.

DESCRIPTION OF THE INVENTION

[0005] The term "active substance" for the purposes of this invention refers to any pharmacologically effective compound which (as such or in the form of the pharmaceutically acceptable salts thereof) is a weak base and in the range from pH 1 to pH 7.5 exhibits pH-dependent solubility characteristics (with greater solubility under acidic conditions and less solubility under basic conditions). In these active substances, in fact, the bioavailability may be dependent on the pH in the gastrointestinal tract when administered orally. Preferably, active substances in the sense of this invention have a relatively high saturation solubility in aqueous solutions at low pH levels as a result of single or multiple protonation, whereas at pH values above 5 the neutral compounds are virtually insoluble according to the definition in the European Pharmacopoeia (saturation solubility less than 100 µg/ml).

[0006] The oral formulation according to the invention may contain as active substance for example ethyl 3-[(2-{4-(hexyloxy-carbonylamino-imino-methyl)-phenylamino}-methyl)-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino]-propionate (WO 98/37075), BIBU 104 (Lefradafiban; (3S,5S)-5-[[4'-(N-methoxycarbonylamidino)4-biphenyl]-oxy-methyl]-3-[(methoxycarbonyl)-methyl]-2-pyrrolidinone; EP 0 483 667), (R)-2-[4-(N-phenyl-carbonylamidino)-phenylaminomethyl]-1-methyl-5-[1-(n-propyloxycarbonyl-methylamino)-1-(pyrrolidinocarbonyl)-ethyl]-benzimidazole (WO 01/47896), telmisartan, DTTX 30 SE, BIBV 308 SE (terbogrel), bromhexine, BIIL 284 (amelubant; 4-((3-((4-(1-(4-hydroxyphenyl)-1-methylethyl)phenoxy)methyl)benzyl)oxy)benzenecarboximidamid-N-ethylcarboxylate; WO 96/02497), flibanserine (1-[2-(4-(3-trifluoromethyl-phenyl)piperazin-1-yl)ethyl]-2,3-dihydro-1H-benzimidazol-2-one; EP-A-526434;), 4-(4-(2-pyrrolylcarbonyl)-1-piperazinyl)-3-trifluoromethyl-benzoylguanidine (WO 00/17176), pimobendane or one of the pharmacologically acceptable salts of these compounds (such as the hydrochlorides, hydrobromides, mesylates, sulphates and phosphates).

[0007] The solubility of a compound may be determined by dispersing an excess of the compound at ambient tem-

perature in the medium in question and shaking it vigorously for a defined length of time (approx. 1 to 24 h) until equilibrium is achieved. After filtration the pH is determined in the clear filtrate and the concentration of the dissolved substance is determined by spectral photometry or some other suitable analytical process.

[0008] The pH-dependent solubility characteristics of the active substance may mean that, depending on the dose, when administered orally in solid preparations of conventional composition, the active substance is only totally dissolved in the patient's stomach if the liquid present in the stomach has a low enough pH. If the pH in the stomach is elevated (this may be the result of normal physiological variability, illness or co-medication with pharmaceutical compositions that raise the gastric pH), the active substance may not dissolve totally.

[0009] The effect of the dose of the active substance on its bioavailability can be quantitatively described by means of the concept of the (dimensionless) dose number (Do). The dose number is defined as:

$$Do = (Mo/Vo)/Cs,$$

[0010] where

[0011] Mo=dose (mg),

[0012] Vo=liquid volume present (ml) and

[0013] Cs=saturation solubility (mg/ml).

[0014] According to an assumption which is conventional nowadays the liquid volume in the stomach after taking a preparation is about 250 ml. (Löbenberg, R., Amidon, G. L.: Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards (Eur. J. Pharm. Biopharm. 50 (2000) 3-12).

[0015] At dosages which give a dose number of less than 1, no solubility problems occur. Only if the critical dose number of 1 is exceeded may there be significant reductions in solubility and hence a decreased bioavailability. As a rule the actual problem area only begins at doses which give a dose number significantly above 1, as at least some of the dissolved substance is constantly eliminated from the equilibrium by the absorption process.

[0016] The active substances contained in the oral formulation according to the invention have a value of less than 1 for the dose number, based on the solubility at pH<2 (i.e. a sufficiently acidic stomach) and a value significantly above 1 for the dose number based on the solubility at pH>5 (i.e. no or vanishingly low gastric acid), i.e. for the oral formulation according to the invention both the degree of pH-dependence of the solubility of the active substance and the size of the dose of active substance are of interest.

[0017] Raising the gastric pH in the case of active substances with solubility characteristics of this kind may then lead to a substantially reduced bioavailability of the active substance (even amounting to total malabsorption) which in some cases results in failure of the treatment. Generally increasing the dose in order to compensate for the reduced bioavailability in patients with a raised gastric pH is frequently undesirable because of the waste of active substance and the greater burden on the patient and the associated risk of side effects, for example, or even totally impossible, on the grounds of drug safety.

[0018] The aim of the invention is to provide a pharmaceutical composition for oral administration of active substances with pH-dependent solubility characteristics which guarantees largely pH-independent bioavailability of the active substance.

[0019] It has now been found that the use of pharmaceutically acceptable organic acids with a water solubility of more than 1 g/250 ml at 20° C., preferably more than 1 g/160 ml at 25° C., in solid oral formulations can ensure sufficient bioavailability of active substances with pH-dependent solubility characteristics, even in patients with a raised gastric pH.

[0020] Pharmaceutically suitable acids for the purposes of this invention are for example tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid including the hydrates and acid salts thereof. Particularly suitable for the purposes of this invention are tartaric acid, fumaric acid, succinic acid and citric acid, particularly tartaric acid, fumaric acid and succinic acid.

[0021] Numerous active substances display a more or less marked tendency to hydrolytic decomposition in the presence of acids and traces of water. In individual cases there may even be a direct chemical reaction between the active substance and organic acids, e.g. ester formation. When developing a product which remains stable when stored it is therefore advantageous to separate the organic acid spatially from the active substance in the formulation. Only after the administration of the formulation does the organic acid dissolve and produce an acidic microclimate in which the active substance can dissolve.

[0022] A further aim of the invention is to prevent the undesirable interactions between acid and active substance in spite of the use of an organic acid to improve the solubility.

[0023] Multiparticulate formulations in which the individual particles have the structure shown in FIG. 1 are particularly suitable for the preferred spatial separation of active substance and organic acid.

[0024] FIG. 1 shows the diagrammatic structure of the pharmaceutical composition by means of a section through a pellet which is suitable for producing the pharmaceutical composition according to the invention. The roughly bead-shaped/spherical core portion of this pellet contains or consists of the pharmaceutically acceptable organic acid. This is optionally followed by a layer which separates the acid core from the layer containing the active substance, the so-called insulating layer. The insulating layer in turn, or the core material in the absence of an insulating layer, is surrounded by the active substance layer, which is also spherical, which may itself be surrounded by a coating to increase the abrasion resistance and shelf life of the pellets.

[0025] The core material used is a pharmaceutically acceptable organic acid with a water solubility of >1 g/250 ml at 20° C., such as e.g. tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid including the hydrates and acid salts thereof, to which a small amount of 1 to 10% by weight, preferably 3 to 6% by weight of a suitable binder is optionally added. The use of a binder may be necessary, for example, if the starting acids are produced by a pan build-up process. If the method used is extrusion or spheronisation, other technological adjuvants

such as microcrystalline cellulose will be needed instead of binders. It is also possible to use pure (100%) acid as the starting material if it can be obtained in a sufficiently narrow range of particle sizes. The pharmaceutically acceptable organic acids used are preferably tartaric acid, fumaric acid, succinic acid or citric acid; tartaric acid is particularly preferred. As binder, it is possible to use gum arabic or a partially or totally synthetic polymer selected from among the hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, polyvinylpyrrolidone, the copolymers of N-vinylpyrrolidone and vinyl acetate, or combinations of these polymers; gum arabic is preferred. The spherical core material preferably has an average diameter of 0.4-1.5 mm. The content of the pharmaceutically acceptable organic acid is usually between 30 and 100% in the core material.

[0026] To increase the durability of the finished product it is advantageous to coat the core material before the application of the active substance with an insulating layer based on a water-soluble, pharmaceutically acceptable polymer. Examples of such water-soluble polymers include for example gum arabic or a partially or totally synthetic polymer selected from among the hydroxypropylcelluloses, hydroxypropylmethylcelluloses, methylcelluloses, hydroxyethylcelluloses, carboxymethylcelluloses, polyvinylpyrrolidone, the copolymers of N-vinylpyrrolidone and vinyl acetate, or combinations of these polymers. Gum arabic or a hydroxypropylmethylcellulose is preferably used. If desired, the coating with the water-soluble, pharmaceutically acceptable polymer may be carried out with the addition of suitable plasticisers, separating agents and pigments, such as for example triethylcitrate, tributylcitrate, triacetin, polyethyleneglycols (plasticisers), talc, silicic acid (separating agents), titanium dioxide or iron oxide pigments (pigments).

[0027] The active substance layer contains the active substance as well as binders and optionally separating agents. Suitable binders include for example hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate or combinations of these polymers. Preferably, hydroxypropylcellulose or copolymers of N-vinylpyrrolidone and vinyl acetate are used. The addition of separating agents such as e.g. talc, magnesium stearate or silicic acid serves to prevent the particles from aggregating during the process. The preferred active substance content is not more than 60%, preferably not more than 50% of the pharmaceutical composition.

[0028] The optional outermost layer, which serves to reduce any increased abrasion during packing into capsules and/or to increase the shelf life, consists of pharmaceutically conventional film-forming agents, plasticisers and optionally pigments. Suitable film-forming agents include for example hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, polymers and copolymers of acrylic and methacrylic acid and the esters thereof, or combinations of these polymers. Suitable plasticisers include inter alia triethylcitrate, tributylcitrate, triacetin or polyethyleneglycols. The pigments used may be e.g. titanium dioxide or iron oxide pigments. Preferably, the outer coating consists of

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hydroxypropylmethylcellulose and/or methylcellulose, optionally with the addition of polyethyleneglycols as plasticisers.

[0029] The pellets may be prepared by the method described hereinafter:

[0030] The acid-containing core material consists either of crystals of the particular organic acid used or, more advantageously, of roughly spherical particles of the desired size containing a large amount of organic acid, which can be produced by methods known and established in pharmaceutical technology. The core material may be produced, in particular, by pan methods, on pelleting plates or by extrusion/spheronisation. Then the core material thus obtained may be divided into fractions of the desired diameter by screening. Suitable core material has an average diameter of 0.4 to 1.5 mm, preferably 0.6 to 0.8 mm.

[0031] First, the insulating layer is applied to this acid-containing core material. This can be done by conventional methods, e.g. by applying an aqueous dispersion of the water-soluble, pharmaceutically acceptable polymer, optionally with the addition of plasticisers, separating agents and/or pigments, in a fluidised bed, in coating pans or in conventional film coating apparatus. If necessary the product can then be screened again.

[0032] Then the active substance is applied from a dispersion containing binder and optionally separating agent. The volatile dispersant is removed during or after the process by drying. Suitable binders in the dispersion may be for example hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl acetate or combinations of these polymers. Preferably, hydroxypropylcellulose or copolymers of N-vinylpyrrolidone and vinyl acetate are used. Suitable separating agents include e.g. talc, magnesium stearate or silicic acid; preferably, talc is used. The dispersants may be for example water, ethanol, 2-propanol, acetone or mixtures of these solvents with one another. The application of active substance to the core material may be carried out by established methods known in pharmaceutical technology, e.g. in coating pans, conventional film coating apparatus or by the fluidised bed method. Then a further screening process may be carried out.

[0033] To reduce any increased abrasion during transfer into capsules or to increase the shelf life the system may finally be coated with a coating of a pharmaceutically conventional film forming agent, plasticiser and optionally pigment. This may be done by conventional methods as mentioned earlier in the description of the application of the insulating layer.

[0034] When core material with an average diameter of 0.4-1.5 mm is used, the process described above produces pellets containing active substance, which can then be packed into hard capsules, for example. To do this, a number of these units corresponding to the required dosage are packed into hard capsules in a standard capsule filling machine. Suitable hard capsules include, for example, hard gelatine capsules or hard capsules of hydroxypropylmethylcellulose (HPMC). The preferred active substance content of the pharmaceutical composition is not more than 60%, preferably not more than 50%.

[0035] Unless otherwise stated, percentages specified are always percent by weight. All the data on the active substance content relate to the active substance base unless otherwise stated.

[0036] As already mentioned, the pharmaceutical compositions according to the invention exhibit improved bioavailability of the active substance contained therein. For example, the pharmaceutical compositions according to Examples 1 and 2 were tested for the improvement to the bioavailability.

[0037] Results of the Clinical Trials

[0038] To do this, the formulation prepared according to Example 1 was clinically tested for its bioavailability on a total of 15 volunteers. In one branch of the treatment, the volunteers were given the composition by mouth (=orally) on an empty stomach without any pre-treatment. In another branch of the treatment the same volunteers were pre-treated, prior to the oral administration of the composition, with 40 mg of pantoprazole b.i.d. (=twice a day) for three days by mouth to increase the gastric pH; the treatment with pantoprazole was continued during the administration of the formulation according to the invention.

[0039] The degree of absorption was determined by measuring the quantity of active metabolite 3-[(2-[[4-(amino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid excreted in the urine.

[0040] The relative bioavailability after pre-treatment with pantoprazole was 94% on average compared with administration without any pre-treatment.

[0041] Under comparable conditions of administration, the relative bioavailability (based on the area under the plasma concentration/time curve) of a tablet containing 50 mg of active substance, developed and produced according to the prior art and containing no water-soluble organic acid, after corresponding pre-treatment with pantoprazole, is 18%. The following list shows the precise composition of the tablet used:

TABLE 1

Ingredient	mg/tablet
<u>Core</u>	
ethyl 3-[(2-[[4-(hexyloxy-carbonyl-amino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate	57.7
lactose monohydrate	58.0
microcrystalline cellulose	48.3
crospovidone	3.4
magnesium stearate	2.6
<u>Film coating</u>	
polyethyleneglycol 6000	0.56
titanium dioxide	0.80
talc	0.64
hydroxypropylmethylcellulose	1.92
iron oxide yellow	0.08
Total	174.0

[0042] The bioavailability was thus improved by about a factor of 5 by using the formulation according to the invention.

[0043] The formulation prepared according to Example 2 was also clinically tested for its bioavailability on a total of 15 volunteers. In one branch of the treatment, the volunteers were given the composition by mouth on an empty stomach without any pre-treatment. In another branch of the treatment the same volunteers were pre-treated, prior to the oral administration of the composition, with 40 mg of pantoprazole b.i.d. for three days by mouth to increase the gastric pH; the treatment with pantoprazole was continued during the administration of the formulation according to the invention.

[0044] The degree of absorption was determined by measuring the quantity of the active metabolite 3-[(2-[[4-(amino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionic acid excreted in the urine.

[0045] The relative bioavailability after pre-treatment with pantoprazole was 76% on average compared with administration without any pre-treatment.

[0046] Under comparable conditions of administration, the relative bioavailability (based on the area under the plasma concentration/time curve) of a tablet containing 50 mg of active substance, developed and produced according to the prior art and containing no water-soluble organic acid, after corresponding pre-treatment with pantoprazole, is 18%. The following list shows the precise composition of the tablet used:

TABLE 2

Ingredient	mg/tablet
<u>Core</u>	
ethyl 3-[(2-[[4-(hexyloxycarbonyl-amino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate	57.7
lactose monohydrate	58.0
microcrystalline cellulose	48.3
crospovidone	3.4
magnesium stearate	2.6
<u>Film coating</u>	
polyethyleneglycol 6000	0.56
titanium dioxide	0.80
talc	0.64
hydroxypropylmethylcellulose	1.92
iron oxide yellow	0.08
Total	174.0

[0047] The bioavailability of the active substance compared with conventional formulations was thus improved by about a factor of 4 by using the formulation according to the invention.

[0048] FIG. 2 graphically illustrates the bioavailability of the formulations according to the invention compared with the conventional tablet with and without the administration of pantoprazole.

[0049] The amount of active substance per capsule is preferably selected so that taking 1 to 2 capsules a day is sufficient to achieve the desired activity.

[0050] The preferred ratio of acid to active substance is about 1:1 to approx. 20:1. The theoretical lower limit at

which the system can still function is 1 equivalent of acid per mol of active substance. The upper limit of approximately 20:1 (acid to active substance) is determined by the size of the formulation at the desired dosages (number of pellets per capsule).

[0051] In quality control, in vitro releases are measured by USP methods. The drug is released in a volume of 900 ml and the pH is selected so as to obtain "sink conditions", i.e. the entire dose of active substance is soluble in these 900 ml. This in vitro method cannot be predictive of absorption in humans as a patient will generally take the drug with approx. 200 ml of liquid and in a non-acidic stomach the solubility is often only sufficient for a fraction of the dose. Non-acidic stomach occurs at a rate of about 25% of the population in older patients and is often also caused by co-medication with H2-blockers or proton pump inhibitors.

[0052] Therefore, within the scope of the invention, an empirical test method was developed which has a better correlation with the in vivo performance in humans, particularly in non-acidic stomach. In this procedure, a drug preparation which contains the maximum dose used in humans is released in a volume of 200 ml (this corresponds to the dose in humans) in buffer at a pH with reduced solubility of the active substance in the physiologically relevant range, i.e. between pH 1-7. As the absorbability can also be predicted with some accuracy using this method, even at non-acidic gastric pH levels, it is suitable for optimising drug preparations. In order to identify the most favourable formulation in each case from a number of possible recipes, the maximum release and/or the area under the curve (AUC) from time 0 to the end of the release may be used as relevant characteristics.

[0053] This is clear from the example of the comparison of the formulation examples C2 (reference without acid starter) and C5 (Example according to the invention with tartaric acid starter) (FIG. 3 and Table 3).

[0054] Table 3 shows the in vitro releases and the characteristics of the AUC and maximum release of an Examples C5 according to the invention (active substance: flibanserin; cf. Table 11) compared with the reference form with a similar content of active substance in 0.005 mol citrate buffer pH 5.0

TABLE 3

time (min)	0	2	4	6	10	15	AUC 0-15'	max release	pH*
Example C2	0	8	8	9	9	7	115	9	4.90
Example C5	0	26	61	77	87	89	1018	89	3.45

*This value represents the pH at the end of the release.

[0055] Table 4 shows the in vitro releases and the characteristics of the AUC and maximum release of Examples C4 to C15 according to the invention (active substance: flibanserin; cf. Table 11) compared with the reference forms C1 to C3

TABLE 4

time (mins)	0	2	4	6	10	15	IC 0-	max release	pH*
Example C1	0	8	9	9	9	8	119	9	4.90
Example C2	0	8	8	9	9	7	115	9	4.90
Example C3	0	5	7	8	8	6	97	8	4.29
Example C4	0	65	91	95	97	101	1309	103	2.80
Example C5	0	26	61	77	87	89	1018	89	3.45
Example C6	0	11	19	29	45	50	476	50	3.95
Example C7	0	13	34	53	80	99	884	107	3.00
Example C8	0	5	11	22	55	100	598	100	4.00
Example C10	0	51	79	86	94	97	1182	97	3.98
Example C11	0	7	16	27	33	40	371	40	3.95
Example C14	0	26	77	88	91	93	1113	93	3.35
Example C15	0	16	36	37	36	37	471	37	3.95

*This value represents the pH at the end of the release.

[0056] Interpretation of the Results:

[0057] All the Examples according to the invention are clearly superior to the reference formulation. As the content of active substance increases the in vitro release declines somewhat, as the amount of acid is smaller for the same dose of active substance.

[0058] All acids and other excipients are generally suitable, but display somewhat different release characteristics at comparable active substance concentrations. Examples C4, C5, C7, C8, C10 and C14 have proved particularly suitable for the purposes of the invention.

[0059] Table 5 shows the in vitro releases and the characteristics of the AUC and maximum release of Examples C18 to C31 according to the invention (active substance: pimobendane; cf. Table 12) compared with reference forms C16 to C17. A 0.005 M citrate buffer adjusted to pH 5.0 was used as the test medium.

TABLE 5

time (mins)	0	2	4	6	10	15	Max	AUC 1 to 15	pH*
Example C16	0	11	11	15	15	14	16	194	5.06
Example C17	0	15	22	25	26	19	26	312	4.85
Example C18	0	53	61	74	87	91	91	1072	3.05
Example C19	0	35	52	59	68	71	71	834	3.2
Example C20	0	26	32	33	42	48	48	523	3.55
Example C21	0	31	51	57	62	66	66	781	3.5
Example C22	0	10	15	19	22	24	24	266	4.1
Example C23	0	6	10	13	15	16	16	179	4.2
Example C24	0	38	46	54	62	80	80	808	2.8
Example C25	0	13	18	26	44	59	59	485	3.55
Example C26	0	10	21	25	30	38	38	366	3.7
Example C27	0	52	73	79	85	85	86	1079	2.85
Example C28	0	19	47	56	64	71	71	765	3.3
Example C29	0	7	19	22	25	26	26	298	3.5
Example C30	0	50	70	78	84	87	87	1071	2.95
Example C31	0	27	42	47	52	54	54	648	3.6

*This value represents the pH at the end of the release.

[0060] Interpretation of the Results:

[0061] All the Examples according to the invention are clearly superior to the reference formulation. As the content of active substance increases the in vitro release declines somewhat, as the amount of acid is smaller for the same dose of active substance.

[0062] All acids and other excipients are generally suitable, but display somewhat different release characteristics at comparable active substance concentrations. Examples C18, C19, C21, C24, C27, C28, C30 and C31 have proved particularly suitable for the purposes of the invention.

[0063] Table 6 shows the in vitro releases and the characteristics of the AUC and maximum release of Examples C35 to C52 according to the invention (active substance: lefradafiban; cf. Table 13) compared with reference forms C32 to C34. A 0.005 M citrate buffer adjusted to pH 5.0 was used as the test medium.

TABLE 6

time (mins)	0	2	4	6	10	15	Max	AUC 1 to 15	pH*
Example C32	0	13	18	15	19	13	21	225	4.95
Example C33	0	10	13	18	17	18	20	218	4.90
Example C34	0	5	6	9	10	10	11	119	4.95
Example C35	0	102	106	101	100	101	106	1418	2.85
Example C36	0	49	75	86	95	94	95	1166	3.35
Example C37	0	8	20	33	33	37	37	395	4.00
Example C38	0	62	77	78	79	83	83	1076	3.50
Example C39	0	16	34	41	41	38	42	498	4.00
Example C40	0	7	10	15	23	24	24	245	4.30
Example C41	0	61	94	98	100	105	105	1318	2.70
Example C42	0	11	26	33	60	74	74	625	3.50
Example C43	0	7	10	16	29	44	44	322	3.90
Example C44	0	97	102	99	100	95	102	1387	2.60
Example C45	0	6	39	66	79	87	87	862	3.40
Example C46	0	4	20	27	33	34	34	367	3.95
Example C47	0	98	98	101	95	99	102	1372	2.75
Example C48	0	40	62	69	69	72	72	904	3.60
Example C49	0	4	13	27	32	32	32	341	3.95
Example C50	0	95	100	101	105	104	106	1426	2.85

TABLE 6-continued

time (mins)	0	2	4	6	10	15	Max	AUC 1 to 15 pH*
Example C51	0	65	59	66	65	67	68	909 3.70
Example C52	0	36	37	39	41	41	42	549 4.05

*This value represents the pH at the end of the release.

[0064] Interpretation of the Results:

[0065] All the Examples according to the invention are clearly superior to the reference formulation. As the content of active substance increases the in vitro release declines somewhat, as the amount of acid is smaller for the same dose of active substance.

[0066] All acids and other excipients are generally suitable, but display somewhat different release characteristics at comparable active substance concentrations. Examples C35, C36, C38, C41, C42, C44, C45, C47, C48, C50, C51 and C52 have proved particularly suitable for the purposes of the invention.

[0067] Table 7 shows the in vitro releases and the characteristics of the AUC and maximum release of Examples C54 to C59 according to the invention (active substance: Amelubant; cf. Table 14) compared with reference form C53. A mixture of water/ethanol was used as the test medium because of the very low solubility of the active substance.

TABLE 7

Time [Min]	0	5	10	15	20	25	30	Max	AUC 1 to 30 pH*
Example C53	0	1	1	1	2	1	3	3	40 7.46
Example C54	0	53	54	55	58	57	62	62	1546 2.46
Example C55	0	34	39	39	41	43	44	44	1086 2.63
Example C56	0	12	12	12	12	12	11	13	335 3.47
Example C57	0	31	49	57	60	68	64	68	1484 2.46

*This value represents the pH at the end of the release.

[0068] Interpretation of the Results:

[0069] All the Examples according to the invention are clearly superior to the reference formulation, while in this case succinic acid starter pellets fare worse than tartaric and fumaric acid.

[0070] Examples C54 to C57 have proved particularly suitable for the purposes of the invention.

[0071] Table 8 shows the in vitro releases and the characteristics of the AUC and maximum release of Examples C60 to C61 according to the invention (active substance: telmisartan; cf. Table 15) compared with reference forms C58 and C59. A 0.0005 M citrate buffer adjusted to pH 5.0 was used as the test medium.

TABLE 8

Time [min]	0	2	4	6	10	15	Max	AUC to 30 pH*
Example C58	0	0	1	2	2	2	2	20.64 5
Example C59	0	0	0	0	0	0	0	4.57 5
Example C60	0	15	20	25	26	24	26	322.11 2
Example C61	0	5	6	7	7	8	8	93.11 2

*This value represents the pH at the end of the release.

[0072] Interpretation of the Results:

[0073] All the Examples according to the invention are clearly superior to the reference formulation.

[0074] As the content of active substance increases the in vitro release declines somewhat, as the amount of acid is smaller for the same dose of active substance.

[0075] Examples C60 and C61 have proved particularly suitable for the purposes of the invention.

[0076] The Examples that follow are intended to illustrate the invention:

EXAMPLES

Example 1

[0077]

TABLE 9

	percentage composition				pcr capsule [mg]
	core material	insulating layer	active substance layer	total	
tartaric acid	61.3	—	—	61.3	176.7
gum arabic	3.1	2.8	—	5.9	17.0
talc	—	5.6	3.2	8.8	25.4
hydroxypropylcellulose	—	—	4.0	4.0	11.5
active substance (ethyl 3-[(2- {4-(hexyloxy)carbonylamino-	—	—	20.0	20.0	57.7*

TABLE 9-continued

	percentage composition			per capsule [mg]
	core material	insulating layer	active substance layer	
imino-methyl)-phenylamino)-methyl)-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate mesylate)				
total			100.0	288.3

*corresponds to 50 mg of ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (active substance base)

[0078] a) Preparation of Core Material Containing Tartaric Acid

[0079] Composition:

gum arabic	1 part by weight
tartaric acid	20 parts by weight

[0080] 1 part by weight of gum arabic is dissolved with stirring in 4 parts by weight of purified water at 50° C. 5 parts by weight of tartaric acid are then dissolved in this solution with stirring.

[0081] 8.3 parts by weight of tartaric acid crystals with an average particle size of 0.4 to 0.6 mm are placed in a suitable coating apparatus fitted with an air inlet and exhaust and the container is set rotating. At an air inlet temperature of 60°-80° C. the tartaric acid crystals are sprayed with the solution of tartaric acid-gum arabic in intermittent operation and sprinkled with a total of 6.7 parts by weight of powdered tartaric acid, so as to produce roughly spherical particles.

[0082] The spherical tartaric acid core material is then dried in the rotating container at an air inlet temperature of 60°-80° C.

[0083] The core material is fractionated using a tumbler screening machine with perforated plates having nominal mesh sizes of 0.6 and 0.8 mm. The product fraction of between 0.6 and 0.8 mm is used in subsequent processing.

[0084] b) Isolation of the Core Material Containing Tartaric Acid

[0085] Composition:

core material containing tartaric acid	23 parts by weight
gum arabic	1 part by weight
talc	2 parts by weight

[0086] 1 part by weight of gum arabic is dissolved with stirring in a mixture of 6.7 parts by weight of 96% ethanol and 13.5 parts by weight of purified water. Then 2 parts by weight of talc are dispersed in the solution with stirring.

[0087] In a fluidised bed processing plant, 23 parts by weight of tartaric acid-containing core material are sprayed

with the gum arabic/talc dispersion at an air entry temperature of 35°-40° C. by the under-bed spraying method.

[0088] The isolated tartaric acid-containing core material is then dried in the circulating air dryer at 40° C. for 8 hours.

[0089] To remove lumps the dried isolated tartaric acid-containing core material is screened through a screen with a nominal mesh size of 1.0 mm. The fraction of material (particle size less than 1 mm) is further processed.

[0090] c) Preparation of the Active Substance Layer

[0091] Composition:

isolated tartaric acid-containing core material	91 parts by weight
hydroxypropylcellulose	5 parts by weight
talc	4 parts by weight
active substance (mesylate of BIBR 1048)	25 parts by weight

[0092] Hydroxypropylcellulose is dissolved in 168 parts by weight of 2-propanol with stirring and then the active substance and talc are dispersed in this solution with stirring.

[0093] In a fluidised bed processing plant, 91 parts by weight of tartaric acid-containing core material are sprayed with the dispersion containing the active substance at an air entry temperature of 20°-30° C. by the under-bed spraying method.

[0094] The pellets containing the active substance are then dried in the circulating air dryer at 35° C. for 8 hours.

[0095] To remove lumps the pellets containing the active substance are screened through a screen with a nominal mesh size of 1.25 mm. The product fraction (particle size less than 1.25 mm) is further processed.

[0096] d) Packing Into Capsules

[0097] A quantity of pellets containing active substance corresponding to 50 mg of active substance base is packed into size 1 hard gelatine capsules using a capsule filling machine.

Example 2

[0098]

TABLE 10

material	percentage composition			[mg]	per capsule
	core layer	insulating layer	active substance total		
tartaric acid	38.5	—	—	38.5	55.5
gum arabic	1.9	1.7	—	3.6	5.2
talc	—	3.5	6.4	9.9	14.3
hydroxypropylcellulose	—	—	8.0	8.0	11.5
active substance (ethyl 3-[(2- [[4-(hexyloxycarbonylamino- imino-methyl)-phenylamino]- methyl]-1-methyl-1H- benzimidazole-5-carbonyl)- pyridin-2-yl-amino]- propionate mesylate)	—	—	40.0	40.0	57.7*
total				100.0	144.1

*corresponds to 50 mg ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate (active substance base)

[0099] a) Preparation of Core Material Containing Tartaric Acid

[0100] Composition:

gum arabic	1 part by weight
tartaric acid	20 parts by weight

[0101] 1 part by weight of gum arabic is dissolved with stirring in 4 parts by weight of purified water at 50° C. 5 parts by weight of tartaric acid are then dissolved in this solution with stirring.

[0102] 8.3 parts by weight of tartaric acid crystals with an average particle size of 0.4 to 0.6 mm are placed in a suitable coating apparatus fitted with an air inlet and exhaust and the container is set rotating. At an air inlet temperature of 60°-80° C. the tartaric acid crystals are sprayed with the solution of tartaric acid-gum arabic in intermittent operation and sprinkled with a total of 6.7 parts by weight of powdered tartaric acid, so as to produce roughly spherical particles.

[0103] The spherical tartaric acid core material is then dried in the rotating container at an air inlet temperature of 60°-80° C.

[0104] The core material is fractionated using a tumbler screening machine with perforated plates having nominal mesh sizes of 0.6 and 0.8 mm. The product fraction of between 0.6 and 0.8 mm is used in subsequent processing.

[0105] b) Isolation of the Core Material Containing Tartaric Acid

[0106] Composition:

core material containing tartaric acid	23 parts by weight
gum arabic	1 part by weight
talc	2 parts by weight

[0107] 1 part by weight of gum arabic is dissolved with stirring in a mixture of 6.7 parts by weight of 96% ethanol and 13.5 parts by weight of purified water. Then 2 parts by weight of talc are dispersed in the solution with stirring.

[0108] In a fluidised bed processing plant, 23 parts by weight of tartaric acid-containing core material are sprayed with the gum arabic/talc dispersion at an air entry temperature of 35°-40° C. by the under-bed spraying method.

[0109] The isolated tartaric acid-containing core material is then dried in the circulating air dryer at 40° C. for 8 hours.

[0110] To remove lumps the dried isolated tartaric acid-containing core material is screened through a screen with a nominal mesh size of 1.0 mm. The product fraction (particle size less than 1 mm) is further processed.

[0111] c) Preparation of the Active Substance Layer

[0112] Composition:

isolated core material containing tartaric acid	57 parts by weight
hydroxypropylcellulose	10 parts by weight
talc	8 parts by weight
active substance (mesylate of BIBR 1048)	50 parts by weight

[0113] Hydroxypropylcellulose is dissolved in 335 parts by weight of 2-propanol with stirring and then the active substance and talc are dispersed in this solution with stirring.

[0114] In a fluidised bed processing plant, 91 parts by weight of isolated tartaric acid-containing core material are sprayed with the dispersion containing the active substance at an air entry temperature of 20°-30° C. by the under-bed spraying method.

[0115] The pellets containing the active substance are then dried in the circulating air dryer at 35° C. for 8 hours.

[0116] To remove lumps the pellets containing the active substance are screened through a screen with a nominal mesh size of 1.25 mm. The product fraction (particle size less than 1.25 mm) is further processed.

[0117] d) Packing Into Capsules

[0118] A quantity of pellets containing active substance corresponding to 50 mg of active substance base is packed into size 2 hard gelatine capsules using a capsule filling machine.

Further Examples

[0119] The preparation of the following Examples usually takes place over 5 steps:

- [0120] a: preparation of acid-containing core material
- [0121] b: isolation of the acid-containing core material
- [0122] c: preparation of the active substance layer
- [0123] d: isolation of the pellets consisting of acid-containing core
- [0124] e: packing into capsules

[0125] Step b is absolutely essential if there is any incompatibility between acid and active substance layer, otherwise this step may be omitted to simplify the production method. Step d is necessary if the mechanical stability of the active substance layer is insufficient to dissolve the active substance completely.

[0126] a: Examples of the Preparation of Acid-Containing Core Material

Example a1: Preparation of Tartaric Acid-Containing Core Material

[0127] Composition:

gum arabic	1 part by weight
tartaric acid	20 parts by weight

[0128] 1 part by weight of gum arabic is dissolved with stirring in 4 parts by weight of purified water at 50° C. 5 parts by weight of tartaric acid are then dissolved in this solution with stirring.

[0129] 8.3 parts by weight of tartaric acid crystals with an average particle size of 0.4 to 0.6 mm are placed in a suitable coating apparatus fitted with an air inlet and exhaust and the container is set rotating. At an air inlet temperature of 60°-80° C. the tartaric acid crystals are sprayed with the solution of tartaric acid-gum arabic in intermittent operation and sprinkled with a total of 6.7 parts by weight of powdered tartaric acid, so as to produce roughly spherical particles.

[0130] The spherical tartaric acid core material is then dried in the rotating container at an air inlet temperature of 60°-80° C.

[0131] The core material is fractionated using a tumbler screening machine with perforated plates having nominal

mesh sizes of 0.6 and 0.8 mm. The product fraction of between 0.6 and 0.8 mm is used in subsequent processing.

Example a2: Preparation of Fumaric Acid-Containing Core Material

[0132] Composition:

Kollidon K25	3 parts by weight
Avicel PH101	20 parts by weight
fumaric acid	77 parts by weight

[0133] 77 parts by weight of fumaric acid, 20 parts by weight of Avicel PH 101 and 3 parts by weight of Kollidon K25 are mixed for 15 minutes in a gyrowheel mixer. Then the powder mixture is transferred into a twin-screw metering device. This mixture is introduced into a twin-screw extruder of the Werner & Pfleiderer 37/18D type (or any other suitable type of extruder) at a speed of about 1 kg/h, together with water which is added by means of a ProMinent metering pump. The water is automatically regulated so as to obtain a nominal torque of approx. 19% in the extruder. The extrusion is carried out using a die plate with bores 8 mm in diameter.

[0134] The extruded strips are rounded off to form pellets in a WyPro Sphäromat, the process taking approx. 3 minutes at approx. 850 RPM.

[0135] Drying of the pellets at 80° C. for approx. 1.5 h in the GPCG1 fluidised bed dryer.

[0136] The core material is fractionated using a tumbler screening machine with different perforated plates having nominal mesh sizes of 0.71 to 1.25 mm. The suitable fractions of materials of between 0.71 and 0.90 or 0.90 and 1.12 mm are used in subsequent processes.

Example a3: Preparation of Succinic Acid-Containing Core Material

[0137] Composition:

Kollidon K25	3 parts by weight
Avicel PH101	20 parts by weight
succinic acid	77 parts by weight

[0138] 77 parts by weight succinic acid, 20 parts by weight Avicel PH 101 and 3 parts by weight Kollidon K25 are mixed for 15 minutes in a gyrowheel mixer. Then the powder mixture is transferred into a forced mixer. Water is added to this mixture, with stirring, until an extrudable homogeneous mass is formed. This mixture is then further processed analogously to prepare the starter cores containing fumaric acid.

[0139] The product fractions of between 0.71 and 0.90 or 0.90 and 1.12 mm which are suitable in each case are used in the subsequent processes.

Example a4: Preparation of Citric Acid-Containing Core Material

[0140] Composition:

Kollidon K90	1 part by weight
talc	1 part by weight
citric acid	20 parts by weight

[0141] 1 part by weight of Kollidon K90 is dissolved in 6 parts by weight of isopropanol with stirring and 1 part by weight of talc is suspended therein. 3 parts by weight of citric acid are dissolved in another 6 parts by weight of isopropanol, with stirring.

[0142] In a fluidised bed processing plant, 17 parts by weight of isolated citric acid-containing core material measuring 0.5-0.6 mm are sprayed with the two dispersions/solutions containing the active substance at an air entry temperature of 20°-30° C. by the under-bed spraying method, using a three-headed nozzle, so as to obtain substantially spherical particles.

[0143] The pellets containing the active substance are then dried in the circulating air dryer at 35° C. for 8 hours.

[0144] The spherical tartaric acid core material is then dried in the rotating container at an air inlet temperature of 60°-80° C.

[0145] The core material is fractionated using a tumbler screening machine with perforated plates having nominal mesh sizes of 0.6 and 0.8 mm. The product fraction between 0.6 and 0.8 mm is used for further processing.

[0146] b: Example of the Isolation of the Acid-Containing Core Material

[0147] Composition:

acid-containing core material	23 parts by weight
gum arabic	1 part by weight
talc	2 parts by weight

[0148] 1 part by weight of gum arabic is dissolved with stirring in a mixture of 6.7 parts by weight of 96% ethanol and 13.5 parts by weight of purified water. Then 2 parts by weight of talc are dispersed in the solution with stirring.

[0149] In a fluidised bed processing plant, 23 parts by weight of acid-containing core material are sprayed with the gum arabic/talc dispersion at an air entry temperature of 35°-40° C. by the under-bed spraying method.

[0150] The isolated tartaric acid-containing core material is then dried in the circulating air dryer at 40° C. for 8 hours.

[0151] To remove lumps the dried isolated tartaric acid-containing core material is screened through a screen with a nominal mesh size of 1.0 mm. The fraction of material (particle size less than 1 mm) is further processed.

[0152] c: Examples of the Preparation of the Active Substance Layer

[0153] The active substance layer is generally prepared in the same way, but with variations in the nature and quantity of the active substance, the nature and quantity of the binder, the amount of talc and isopropanol or the amount of ethanol. The preparation is therefore only described for Example C4, and the particular compositions for each active substance are shown in table form.

[0154] Preparation of Example C4:

[0155] Composition:

isolated tartaric acid-containing core material	74 parts by weight
hydroxypropylcellulose	49 parts by weight
talc	12 parts by weight
active substance (e.g. fibanserin)	25 parts by weight

[0156] Hydroxypropylcellulose is dissolved in 492 parts by weight of 2-propanol with stirring and then the active substance and talc are dispersed in this solution with stirring.

[0157] In a fluidised bed processing plant, 74 parts by weight of isolated tartaric acid-containing core material are sprayed with the dispersion containing the active substance at an air entry temperature of 20°-30° C. by the under-bed spraying method.

[0158] The pellets containing the active substance are then dried at 35° C. in the circulating air dryer for 8 hours.

[0159] To remove lumps the pellets containing the active substance are screened through a screen with a nominal mesh size of 1.25 mm. The product fraction (particle size less than 1.25 mm) is further processed.

[0160] Table 11 shows the composition of Examples C1-C15 (active substance fibanserin). In each case parts by weight are specified which correspond to the active substance content determined experimentally, i.e. the spray losses, which may fluctuate somewhat from one batch to the next, were compensated in the calculation in each case so as to obtain truly comparable data.

[0161] Examples C1-C3 contain a commercially available neutral core instead of the acid-containing starter cores according to the invention. These cores serve as reference values for the in vitro testing (see above).

[0162] Table 12 shows the composition of Examples C16-C31 (active substance pimobendane). In each case parts by weight are specified which correspond to the active substance content determined experimentally, i.e. the spray losses, which may fluctuate somewhat from one batch to the next, were compensated in the calculation in each case so as to obtain truly comparable data.

[0163] Examples C16-C17 contain a commercially available neutral core instead of the acid-containing starter cores according to the invention. These cores serve as reference values for the in vitro testing (see above).

[0164] Table 13 shows the composition of Examples C32-C52 (active substance lefradafiban, BIBU 104). In each case

parts by weight are specified which correspond to the active substance content determined experimentally, i.e. the spray losses, which may fluctuate somewhat from one batch to the next, were compensated in the calculation in each case so as to obtain truly comparable data.

[0165] Examples C32-C34 contain a commercially available neutral core instead of the acid-containing starter cores according to the invention. These cores serve as reference values for the in vitro testing (see above).

[0166] Table 14 shows the composition of Examples C53-C57 (active substance BIIL 284=amelubant). In each case parts by weight are specified which correspond to the active substance content determined experimentally, i.e. the spray losses, which may fluctuate somewhat from one batch to the next, were compensated in the calculation in each case so as to obtain truly comparable data.

[0167] Example C53 contains a commercially available neutral core instead of the acid-containing starter cores according to the invention. This core serves as a reference value for the in vitro testing (see above).

[0168] Table 15 shows the composition of Examples C58-C61 (active substance pimobendane). In each case parts by weight are specified which correspond to the active substance content determined experimentally, i.e. the spray losses, which may fluctuate somewhat from one batch to the next, were compensated in the calculation in each case so as to obtain truly comparable data.

[0169] Examples C58-C59 contain a commercially available neutral core instead of the acid-containing starter cores according to the invention. These cores serve as reference values for the in vitro testing (see above).

TABLE 11

	neutral pellets	tartaric acid pellets	succinic acid acid pellets	fumaric acid pellets	fliban- serine	povidone K25	talc	Klucel EF	isopropanol (only for preparation)	active substance content [%]
Example C1	200				17		8	4	268	6.9
Example C2	200				76		38	19	885	22.7
Example C3	200				127		64	32	1272	31.4
Example C4		200			35		17	9	348	12.6
Example C5		200			89		44	22	888	24.8
Example C6		200			204		102	51	2040	37.7
Example C7				200	43		22	11	432	14.9
Example C8				200	96		48	24	960	24.7
Example C9				200	170		85	43	1704	34.6
Example C10			200		22		11	5	216	9.2
Example C11			200		84		42	21	840	22.7
Example C12			200		168		84	42	1680	36.5
Example C13			200		31	4	16		488	11.9
Example C14			200		84	11	42		999	24.4
Example C15			200		156	20	78		1454	35.5

[0170]

TABLE 12

	neutral pellets	tartaric acid starter	succinic acid starter	fumaric acid starter	pimo- bendane	povidone K90	talc	Klucel EF	isopropanol (only for preparation)	active substance content [%]
Example C16	200				10	3	5		14	5
Example C17	200				28	9	14		38	11
Example C18		200			12	4	6		16	5
Example C19		200			30	10	15		40	11
Example C20		200			55	18	27		73	18
Example C21			200		13	4	6		17	5
Example C22			200		41	14	20		54	14
Example C23			200		62	21	31		83	21
Example C24				200	16	5	8		21	7
Example C25				200	30	10	15		40	12
Example C26				200	81	27	41		108	24
Example C27		200			10		5	3	13	4
Example C28		200			33		17	11	46	12
Example C29		200			45		23	15	60	16
Example C30		200			13	2	6	2	17	5
Example C31		200			37	6	19	6	50	13

[0171]

TABLE 13

	neutral pellets	citric acid starter	tartaric acid starter	succinic acid starter	fumaric acid starter	lefradafiban	povidone K90	talc	Klucel EF	isopropanol (only for preparation)	exp. active substance content [%]
Example C32	200					28	9	14		184	10.8
Example C33	200					94	31	47		624	25.3
Example C34	200					163	54	82		1088	33.3
Example C35			200			28	9	14		184	10.9
Example C36			200			82	27	41		544	23.1
Example C37			200			160	53	80		1064	33.5
Example C38				200		24	8	12		160	10.1
Example C39				200		82	27	41		544	23.3
Example C40				200		163	54	82		1088	32.7
Example C41					200	24	8	12		160	9.8
Example C42					200	86	29	43		576	23.6
Example C43					200	94	31	47		624	32.1
Example C44			200			22		11	7	144	9.0
Bespiel C45			200			82		41	27	544	22.8
Example C46			200			175		88	58	1168	33.5
Example C47			200			24	4	12	4	160	10.5
Example C48			200			94	16	47	16	624	24.8
Example C49			200			192	32	96	32	1280	34.7
Example C50		200				24	8	12		160	9.8
Example C51		200				82	27	41		544	23.4
Example C52		200				175	58	88		1168	34.4

[0172]

TABLE 14

	neutral pellets	citric acid starter	tartaric acid starter	succinic acid starter	fumaric acid starter	amelubant	Povidone K90	talc	Klucel EF	isopropanol (only for preparation)	exp. active substance content
Example C53	200					13	3	3		104	6
Example C54			200			23	5	5		184	10
Example C55			200			48	10	10		384	18
Example C56				200		38	8	8		304	15
Example C57					200	33	7	7		264	13

[0173]

TABLE 15

	neutral pellets	citric acid starter	tartaric acid starter	succinic acid starter	fumaric acid starter	telmisartan	Povidone K90	talc	Klucel EF	isopropanol (only for preparation)	exp. active substance content
Example C58	200					7 18	2	3 9		85	3
Example C59	200					7	4	3		220	8
Example C60			200			20	2	10		85	3
Example C61			200				5			250	9

[0174] d: Example of the Isolation of the Pellets Containing Active Substance

[0175] Composition:

pellets containing active substance	23 parts by weight
gum arabic	1 part by weight
talc	2 parts by weight

[0176] 1 part by weight of gum arabic is dissolved with stirring in a mixture of 6.7 parts by weight of 96% ethanol and 13.5 parts by weight of purified water. Then 2 parts by weight of talc are dispersed in the solution with stirring.

[0177] In a fluidised bed processing plant, 23 parts by weight of active substance-containing core material are sprayed with the gum arabic/talc dispersion at an air entry temperature of 35°-40° C. by the under-bed spraying method.

[0178] The isolated tartaric acid-containing core material is then dried in the circulating air dryer at 40° C. for 8 hours.

[0179] To remove lumps the dried active substance-containing pellets are screened through a screen with a nominal mesh size of 1.25 mm. The product fraction (particle size less than 1.25 mm) is further processed.

[0180] e) Packing Into Capsules

[0181] A quantity of pellets containing active substance corresponding to the desired dosage in each case is packed into hard gelatine capsules of suitable size using a capsule filling machine.

1. Pharmaceutical composition with a bioavailability of the active substance which is substantially independent of the gastric pH, for oral administration of active substances with pH-dependent solubilities and a dose number of more than 1 at a pH>5, comprising a plurality of pellets synthesised in each case from

- a) a core material,
- b) an optional insulating layer,
- c) an active substance layer and
- d) an optional coating,

wherein the core material consists of one or more pharmaceutically acceptable organic acid(s) with a water solubility of more than 1 g/250 ml at 20° C., optionally with the addition of binders or other technological adjuvants.

2. Pharmaceutical composition according to claim 1, wherein the pharmaceutically acceptable organic acid is chosen from tartaric acid, fumaric acid, succinic acid, citric acid, malic acid, glutamic acid and aspartic acid or one of the hydrates or acid salts thereof.

3. Pharmaceutical composition according to claim 2, characterised in that the pharmaceutically acceptable organic acid is chosen from tartaric acid, fumaric acid, citric acid or succinic acid.

4. Pharmaceutical composition according to claim 2, characterised in that the pharmaceutically acceptable organic acid is tartaric acid.

5. Pharmaceutical composition according to claim 1, wherein the binder is selected from the group comprising the hydroxypropylcelluloses, the hydroxypropylmethylcelluloses, the methylcelluloses, the hydroxyethylcelluloses, the carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate or combinations of these polymers.

6. Pharmaceutical composition according to claim 1 wherein the core material has an average particle size of 0.4 to 1.5 mm.

7. Pharmaceutical composition according to claim 1, wherein the insulating layer consists of a water-soluble polymer, optionally with the addition of suitable plasticisers, separating agents and pigments.

8. Pharmaceutical composition according to claim 7, wherein said water-soluble polymer consists of gum arabic or a partially or totally synthetic polymer selected from among the hydroxypropylcelluloses, the hydroxypropylmethylcelluloses, the methylcelluloses, the hydroxyethylcelluloses, the carboxymethylcelluloses, the polyvinylpyrrolidones, the copolymers of N-vinylpyrrolidone and vinyl acetate or combinations of said polymers.

9. Pharmaceutical composition according to claim 1, wherein the coating consists of film-forming agents, plasticisers and optionally pigments.

10. Pharmaceutical composition according to claim 1 wherein said pellets containing active substance are packed into hard capsules.

11. Process for preparing a pharmaceutical composition for oral administration containing an active substance with pH-dependent solubility characteristics and a dose number >>1 at pH>5 or one of the physiologically acceptable salts thereof, comprising the steps of:

- a) synthesising the core material from one or more pharmaceutically acceptable organic acid(s) with a water solubility of more than 1 g/250 ml at 20° C., optionally with the addition of binders or other technological adjuvants, by pan methods, on pelleting plates or by extrusion/spheronisation,
- b) applying an insulating layer consisting of one or more water-soluble, pharmaceutically acceptable polymers, optionally with the addition of plasticisers, separating agents and/or pigments, to the core material,
- c) applying the active substance from a dispersion containing binder and optionally separating agent, and simultaneously or subsequently drying to eliminate the dispersing agent,
- d) optionally applying a coating of film-forming agents, plasticisers and optionally pigments and
- e) packing the pellets containing active substance thus obtained into hard capsules.

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