Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 04-067463 -00005-0000
Fec. 2005-09-30 15:27:02 Dep 2020 NUECREACIONES
Tra 11 PATENTEYM
Eve 379 FASENACIONALII
Act 4m

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A

- [x] Patente de Invención
- [ ] Patente de Modelo de Utilidad
- [ ] Diseño Industrial
- [ ] Esquema de Trazado para Circuitos Integrados
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente. 04-067463
Solicitante NOVARTIS AG.
Apoderado PROCAPS S.A.
Título de la nueva creación o denominación del signo "COMPOSICIONES FARMACEÚTICAS DE AGONISTA PARCIAL DE 5HT4."
Gaceta 564

③ OPOSICIÓN PRESENTADA POR.

SOLICITANTE

Nombre PROCAPS S A
Dirección CALLE 80 No 78b-201
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución BARRANQUILLA
Teléfono 371 99 00 Fax 373 08 18
E mail

IDENTIFICACIÓN
CC [ ] NIT [x]
CE [ ] Otro [ ]
Cual
Número 890.106.527-5

REPRESENTANTE O APODERADO

Nombre REINALDO PINILLA MORENO
Dirección TRANSVERSAL 13 A #119-95 OFICINA 104
Teléfono 2131213 Fax 6121979
E mail negocios@optimum-co.com

IDENTIFICACIÓN
CC [x] NIT [ ]
CE [ ] Otro [ ]
Cual
Número 80.425.609 TP 91563

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 o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos"

2000-F04

⑤ **Comprobante de pago No** _____ **Fecha** _____

⑥ **ANEXOS**

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

⑦

NOMBRE. REINALDO PINILLA MORENO

FIRMA.

C.C 80425609 **TP** 91563 CSJ

PRESENTACION PERSONAL

En Bogotá D C a 29 AGO 2006 se presentó

en la Notaría Décima cuyo titular es SERGIO FRANCO LEON

REINALDO PINILLA MORENO

Con cédula No 80425609 TP 91563

Expedida en USAQUEN y dijo que

el anterior documento es cierto y que la firma es de su puño y

letra En constancia se firma

REPUBLICA DE COLOMBIA
NOTARIO DECIMO
DE BOGOTA
SERGIO FRANCO LEON

Instrucciones para el diligenciamiento del presente formulario ver reverso de esta página

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S D

Referencia	: Expediente N° 04 067.463
Asunto	: Oposición a la solicitud de patente de Invención titulada "COMPOSICIONES FARMACÉUTICAS DE AGONISTA PARCIAL DE 5HT$_4$"
Solicitante	: NOVARTIS AG
Opositora	:PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 564 del 31 de Mayo de 2006

Yo, *REINALDO PINILLA MORENO* abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura en mi condición de apoderado de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla Colombia atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada presento oposición a la concesión del registro de la patente de Invención titulada *"COMPOSICIONES FARMACÉUTICAS DE AGONISTA PARCIAL DE 5HT$_4$"* solicitada por *NOVARTIS AG* 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 tegaserod 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 7 de diciembre de 2005 reivindicando prioridad bajo la solicitud EP20010403339 del 2001 12-21 y fue publicada en Colombia en la Gaceta de la Propiedad Industrial Nº 564 del 31 de Mayo de 2006 página 401 Nº publicación 102 cuya publicación internacional corresponde a la WO03053432 del 2003-07-03

2 2 La solicitud colombiana 04 067.463 objeto de la presente oposición se refiere a una composición farmacéutica sólida para administración oral la cual comprende un agonista parcial de 5-HT_4 en forma de base o de sal, en una cantidad de hasta el 10 por ciento en peso un diluyente en una cantidad del 70 al 90 por ciento en

peso un desintegrante en una cantidad menor al 15 por ciento en peso, y en donde las cantidades en peso se basan en el peso total de la composición, donde el agonista parcial de 5-HT_4 es tegaserod donde además comprende un abrillantador, donde la cual además comprende un lubricante donde la cual además comprende un aglutinante donde el tegaserod está en la forma de la sal de maleato Igualmente la solicitud se refiere al proceso para su producción

2 3 Por su parte el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"* Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo Bien pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud

- D1 WO0057857 2000-10-05
- D2 WO0010526 2000-03-02

2 4 Ahora bien el documento D1, se refiere particularmente en el resumen página 6 líneas 5 a 9 ejemplo 6 y reivindicaciones a una tableta para administración oral que se desintegra en la cavidad bucal dentro de 60 segundos, comprendiendo, (i) una cantidad terapéuticamente eficaz de un ingrediente activo (ii) manitol secado por rocío (iii) crospovidona y (iv) uno o varios excipientes farmacéuticamente aceptables Particularmente, la invención se relaciona con una tableta que comprende 5% (p/p) de 5HT_4 cisapride agonista, 77% de manitol, 5% de crospovidona así como dióxido de silicio coloidal, trisilicato de magnesio y estereato de magnesio De esta manera se evidencia que la composición

farmacéutica objeto de protección en la presente solicitud carece de novedad a los ojos de este documento D1 pues este documento anterior revela una misma propuesta anterior como solución que incluye una composición farmacéuticas de agonista parcial de $5HT_4$. Por lo tanto la presente solicitud no es novedosa

2 5 Ahora bien el documento D2 se refiere en la página 2, parágrafo 4 ejemplos 1 y 2 y reivindicaciones a una composición farmacéutica sólida de administración oral que comprende 3% (p/p) de tegaserod (agonista parcial de $5\text{-}HT_4$) 40% de crospovidona y 33% de lactosa Por lo tanto a la luz de la combinación de los documentos D2 con lo expuesto en el documento D1 la solicitud carece de altura o nivel inventivo puesto que cualquier persona versada en la materia puede llegar a derivar de manera obvia, a partir de estos documentos combinados una composición farmacéutica sólida para administración oral la cual comprende un agonista parcial de $5\text{-}HT_4$ en forma de base o de sal, un diluyente y un desintegrante

2 6 En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 04 067.463 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección

2 7 Que por consiguiente respecto a la solicitud pretendida se tiene que

2 7 1 <u>CARECE DE NOVEDAD</u> 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, 21 de diciembre de 2001, ya era conocido pues como se demostró era parte del arte anterior con base en el documento D1 una composición farmacéutica sólida para administración oral la cual comprende un agonista parcial de 5-HT_4 en forma de base o de sal un diluyente y un desintegrante sobre la cual busca protección en el capítulo reivindicatorio

2 7 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 21 de diciembre de 2001, a partir del documento D2 en combinación con D1, es posible deducir la conformación de la composición farmacéutica según lo definido en las reivindicaciones de la presente solicitud

2 8. 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 dos de los tres requisitos de patentabilidad

2 9 Por todo lo anterior atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada

"COMPOSICIONES FARMACÉUTICAS DE AGONISTA PARCIAL DE $5HT_4$", solicitada por *NOVARTIS AG* solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 564

3. PRUEBAS

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

- D1 WO0057857, 2000-10-05
- D2 WO0010526 2000-03-02

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

- D1 WO0057857 2000-10-05
- D2 WO0010526 2000-03-02

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 Transversal 13ª Nº 119-95 Of 104 de esta ciudad de Bogotá

Señor Superintendente

REINALDO PINILLA MORENO
C.C. 80'425 609 de Bogotá
T P.A. 91563 del C S de la J

CCo.

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SUPERINTENDENCIA DE .NDUSTRIA Y COMERCIO

NI" 8001"6089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad 04-087483 -00005-0000
Fec: 2006-08-30 16:27:02 Dep 2020 NUECREACIONES
Tra 11 PATENTELYN
Eve 379 FASENACIONALII

RECIBO DE C AL DE CAJA 06 66,662
FECHA AGOS"O 30 DE "006

C O N S " G N A C I O N

DEPOS TANTE	"IPO PAGO	BANCO	CUEN"A	No PAGO	FECHA PGO	Jr PAGO
.AB PROCAPS	CONSIGNACION	BANCO POPULAR	0.0-00 10 6	483025 0	30"08/2006	390, 00 00
O"ECH L"DA	CONSIGNACION	BANCO POPULAR	050 001 0-6	48609469	.0/08 2006	6,500 00

C O N C E P T O

.AN"	REN"ISTICO	CONCEP"O	TO"AL CONCEPTO
1	5000.-0 -04 PRESENTACION DE OBSER.AC ONES	2 MARCAS Y LEMAS COMERCIA" ES	246,000 00
		OTA. $	246,000

SON DOSC.EN OS CUARENTA Y SE S M L PESOS

RESPONSABLE : _____

RECIBO DE CA.A APL"CADO AL EXPED"EN E No _____

98 15

PROCAPS

PODER ESPECIAL

Yo **WALTER TANAKA TATEKAWA,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia) por el presente documento otorgo a **REINALDO PINILLA MORENO,** abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No 91563 expedida por el Consejo Superior de la Judicatura, poder especial amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No **04067463** de título **"COMPOSICIONES FARMACÉUTICAS DE AGONISTA PARCIAL DE 5HT4"** de **NOVARTIS** publicada en la gaceta No No 564 del 31 de Mayo de 2006

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

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

Dado y Firmado en Barranquilla (Colombia) a los 28 dias del mes de Julio de 2006

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251 923 de Palmira
Representante Legal

Acepto,

REINALDO PINILLA MORENO
C C. 80 425 609 de Bogotá
T P.A. 91563 del C S. de la J

PRESENTACION PERSONAL

En Bogotá D C a 29 AGO 2006 se presentó

en la Notaría Décima cuyo titular es SERGIO FRANCO LEON

REINALDO PINILLA MORENO

Con cédula No 80425609 TP 91563

Expedida en Usaquén y dijo que

el anterior documento es cierto y que la firma es de su puño y

letra En constancia se firma

REPUBLICA DE COLOMBIA
NOTARIO DECIMO DE BOGOTA D.C.
SERGIO FRANCO LEON

ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que este escrito fue presentado Personalmente por Walter Tanaka Takekawa

Identificado con: 16251923

Expedida en: Palmira

Quien declaró que su contenido es cierto y que la firma puesta en él es suya.

Firma

0 8 AGO. 2006

Huella del Compareciente

REPUBLICA DE COLOMBIA

DE BARRANQUILLA

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag 1

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
11**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS
PROCAPS S A ----------
NIT 890 106 527-5

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

Que por Escritura Pública No 3 615 del 06 de Dic/bre de 1996, t rgada en la N taria 2a de Barranquilla, inscrit (as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el N 67 218 del libro respectivo la sociedad antes mencionada----------

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS

PROCAPS S A ----------

NIT 890 106 527-5

cambio de razon social, por la denominacion LABORATORIOS PROCAPS S A

C E R T I F I C A

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

cambio de razon social por la denominacion PROCAPS S A ----------

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o d cumentos privados

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

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

PROCAPS S A ----------

SIGLA PROCAPS

DOMICILIO PRINCIPAL Barranquilla

NIT No 890 106 527-5

MATRICULA MERCANTIL 24 802

C E R T I F I C A

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

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
11**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS
PROCAPS S A ----------
NIT 890 106 527-5

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

C E R T I F I C A

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

C E R T I F I C A

OBJETO SOCIAL El objeto principal de la sociedad sera a)-La fabricaci n de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario, b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal, c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas,alimenticias y cosmeticas asi como la comercializacion interna y externa de l s productos terminados, d) La compra venta, importaci n exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos quirurgicos,odontologicos y hospitalari s para la salud humana y animal e)La compra,venta exportacion y disdistribucion de dulces, confites galletas y todo tipo de g l sinas o alimentos para el consumo humano f) Actuar como representante o agente de personas naturales y juridicas, naci - naci nales y extranjeras en la realizacion de operaciones transacci nes relacionadas con la industria farmaceutica y en especial c n cualquiera de las actividades descritas en los literales a), b), c) d) y e) antes descritos, g) Prestar los servici s de ases ria y consultoria en las areas administrativas, de mercade , analisis clinico asistencia tecnica, investigacion, c stos y produccion, exportaciones importaciones ventas, relacionadas c n iguales o similares actividades a las que constituyen el objeto de PROCAPS S A , asi como los de publicidad y promocion de product s quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial h)-Adquirir, operar, administrar y explotar, a cualquier titulo empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceutic s, hospitalari s c smeticos En desarrollo de su bjet principal, la sociedad podra tomar interes s cial como acci nista, socio fundador de empresas que tengan igual similar objeto, com-

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

PROCAPS S A ----------
NIT 890 106 527-5

prar vender, ımportar y exportar maquinarias, insumos y repuest s requeridos para el desarrollo de sus actividades tomar dınero en prestamo, fınanciar y garantızar las operaciones comercıales que celebre con terceros relativas a su objeto celebrar y ejecutar todo tıpo de actos y contratos necesarios para desarrollar sus operaciones, gırar, aceptar, otorgar y protestar todo tipo de tıtulos val - res e instrumentos negociables, comprar, vender y constituir gravamenes sobre bıenes muebles e ınmuebles, designar representantes o apoderados en el paıs y en el exterior y en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto socıal y para la mejor proteccion de sus ıntereses corporativos o la de sus socios La sociedad podra garantizar el cumplimiento de obligaciones adquırıdas por terceros o por sus soci s, para lo cual podra inclusive constituir gravamenes reales s bre sus bienes de cualquier naturaleza ----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2 000 000 000	**********2 000 000	**********1 000
Suscrito		
$**********1 220 000 000	**********1 220 000	**********1 000
Pagado		
$**********1 220 000 000	**********1 220 000	**********1 000

C E R T I F I C A

ADMINISTRACION La direccion y administracion de la socıedad c rresponderа a la Asamblea General de Accionıstas, a la Junta Directıva, al Presıdente al Vicepresidente y a un Gerente General Corresponde a la Junta Dırectiva las sıguıentes funcıones y atrıbucıones entre otras Autorizar cualquier acto o contrato cuya cuantıa sea superior al equivalente en pesos Colombıanos a doscientos cincuenta mıl dolares de los Estados Unıdos de America (US$250 000) lıquidados a la tasa de cambıo representativa del mercado vigente el dıa en que se surta la transacion Cuando se trate de operaciones en vırtud de las cuales la socıedad garantıce obligaciones de terceros o de los socios, se requerıra que la operacion sea aprobada con el voto de por l menos 2/3 partes de los ınтegrantes de la Junta Directiva
La s cıedad tendra un Presidente , quien ejercera la representacıon legal de la socıedad y tendra las sıguıentes atribuciones entre otras Ejecutar las decısiones de la Asamblea General de Accionıstas y de la Junta Dırectiva Ejercer la Representacion Legal de la socıedad en todos los actos y contratos que se requıeran para el desarrollo del objeto socıal, de conformıdad con lo prevısto en las leyes y en los presentes estatutos Constıtuir apoderados judıcıales y extrajudıcıales, recıbır notıfıcacı nes, abs lver interrogatorios de parte, confesar obligaciones de la sociedad, transigır, disistır y allanar a la socıedad en cualquıer asunt judıcial Aprobar y celebrar en nombre de la socieda todo acto o c ntrato cuya cuantıa sea ıgual ınferior al equıvalente en pesos colombıanos a doscientos cincuenta mil dolares de l s

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

CAMARA DE COMERCIO DE BARRANQUILLA

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Estados Unidos de America (US$250 000), liquidados a la tasa de cambi representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto Las demas funciones que le correspondan como Representante Legal por disposicion de la ley de estos estatutos o de la Junta Directiva El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal La sociedad tendra un Vicepresidente designado por la Junta Directiva quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta separadamente con el Presidente El vicepresidente tendra las siguentes facultades entre otras Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente Ejercer la representacion legal de la s ciedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogat ri s de parte, confesar obligaciones de la sociedad, transigir desistir y allanar a la sociedad en cualquier asunto judicial Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a cient cincuenta mil dolares de los Estados Unidos de America (US$150 000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fij de la sociedad, inclusive de naturaleza muebles, acci nes, cu tas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravamenes sobre cualquiera de l s anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatut s de la Junta Directiva El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesari para ell acreditar la ausencia del principal La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva El Suplente reemplazara al Gerente General, en sus faltas temporales absolutas o meramente accidentales, quien junto con el gerente general llevaran la representacion legal de la sociedad, c n identicas facultades, pudiendolas ejercer c njunta o separadamente c n el Presidente y Vicepresidente c n identicas facultades que el Gerente General y sin que sea necesari para ello acreditar

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

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la ausencia del titular El Gerente General tendra las siguientes facultades entre otras Ejercer la representacion legal de la s ciedad, en todos los actos y contratos que se requieran para el desarroll del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos Aprobar y celebrar en nombre de la s ciedad todo acto o contrato cuya cuantia sea igual o inferi r al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estad s Unidos de America (US$50 000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad inclusive de naturaleza mueble, acciones, cu tas partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravamenes sobre cualquiera de las anteri res facultades que radican exclusiva y privativamente en cabeza del Presidente ----------

C E R T I F I C A

Que según Acta No 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad
PROCAPS S A ----------
cuya parte pertinente se inscribió en esta Cámara de Comerci , el 15 de Agosto de 1997 bajo el No 70 838 del libro respectivo y según Acta No 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad
PROCAPS S A ----------
cuya parte pertinente se inscribió en esta Cámara de Comercio el 29 de Mayo de 2000 bajo el No 87 250 del libro respectivo, fueron hechos los siguientes nombramientos

CLASE JUNTA DIRECTIVA

Principales

1	Minski Gontovnik Ruben	CC *******7 463 982
2	Minski Gontovnik Meyer	CC *******7 461 324
3	Minski Gontovnik Jose	CC *******8 671 834

Suplentes

1	Minski Zilberblum Elliot	CC ******72 219 541
2	Minski Deitel Daniel	**********
3	Minski Sharon	PA *990 212 082 805

C E R T I F I C A

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

Cargo/Nombre	Identificación
Presidente	
Minski Gontovnik Ruben	CC *******7 463 982

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Suplente del Presidente
Minski Minski Abraham CC *********802 575
Vicepresidente
Minski Gontovnik Meyer CC *******7 461 324
Suplente del vicepresidente
Minski Gontovnik Jose CC *******8 671 834

C E R T I F I C A

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

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

C E R T I F I C A

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

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

C E R T I F I C A

Que según Acta No 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comercio el 04 de Agosto de 1999 bajo el No 82 226 del libro respectivo, fueron hechos los siguientes nombramientos

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

C E R T I F I C A

Que según Acta No 127 del 22 de Marzo de 2000 c rrespondiente a la Asamblea de Accionistas en Barranquilla, de la s ciedad PROCAPS S A cuya parte pertinente se inscribió en esta Cámara de Comerci ,

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el 29 de Mayo de 2000 bajo el No 87 250 del libro respectivo, fueron hechos los siguientes nombramientos

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal	
Lozada Villareal Milena	CC ******32 748 111

C E R T I F I C A

Que por escritura publica No 2 608 del 5 de Octubre del 2 001, torgada en la Notaria 2a de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2 001, bajo los Nos 95 771, 2 056, 2 057, 2 058, 2 059, 2 060, 2 061 2 062 y 2 064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No 3 705 de Noviembre 6 de 1 998 de la Notaria Segunda del Circuito de Barranquilla y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad 1 -Se confiere Poder Especial Amplio y Suficiente a los senores WALTER TANAKA TATEKAWA C C No 16 251 923 WILIIAM ALBERTO BARROS CERRA C C No 8 715 941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S A , suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad asi como para que responda todo tipo de requerimiento o s - licitudes de informacion de las autoridades tributarias aduaneras cambiarias,en los ordenes Distrital, Departamental y Nacional 2 -Se confiere Poder Especial amplio y suficiente,a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US$800 000 oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion GUPO A GUILLERMO LUIS URIBE OCHO C C No 70 073 754 LINO LAZALA SILVA VARGAS C C No 19 260 410, JAIRO MOLINA MEJIA C C No 8 706 380, CLAUDIA TANGARIFE CASTILLO C C No 41 660 - 293 BRUPO B WALTER TANAKA TATEKAWA C C No 16 251 923 HENRY CARO DIAZ C C No 19 395 298, CARMEN ALICIA FLOREZ C C No 22 434 044 CARMEN ALICIA HERRERA DIAZGRANADOS C C No 22 377 540 Para el ejercicio de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B, 3 -Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C C No 33 138 497 a la Doctora MARCELA CARVAJALINO PAGANO C C No 22 579 748, y al Doct r DANIEL MORENO VILLALBA, C C No 19 113 210, para que cada uno representen a PROCAPS S A , ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como Contestar e interponer demandas y requerimientos, comparecer en juicios pedir la practica de pruebas recibir notificaciones,interponer recursos y ejercer acciones contencioso administrativas y de tutela,transigir,conciliar,recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato Para la celebraci n de cualquier acuerdo conciliatorio o transacci nal, judicial extrajudicial, cualquiera que sea su cuantia,los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la s cie-

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dad Los Apoderados podran presentar solicitudes de devolucion y/ compensacion de impuestos y recibir los pagos por devoluci nes de impuestos, firmar notificarse y realizar todo acto necesario para cumplir con el mandato encomendado ----------

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrit en esta Camara de Comercio el 8 de junio de 2000, bajo el No 1 786 del libro respectivo consta que RUBEN MINSKI GONTOVNIK, C C No 7 463 982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA C C No 32 732 070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS 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 del 13 de diciembre del 2 002, inscrito en esta Camara de Comercio el 15 de enero del 2 003 bajo el N 2 290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C C No 7 463 982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S A , mediante el presente documento otorgo PODER ESPECIAL al Sr MARLON TATIS PAREDES, C C No 72 176 874 para que en representacion de PROCAPS S A , suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/ cualquier entidad del Estado que haga sus veces En consecuencia, el Sr MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S A declaraciones, reportes y cualquier tipo de document s relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces ----------

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2 004, bajo el No 2 753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C C 7 463 982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S A confiere poder especial, ampli y suficiente a ANTONIO VARELA DIAZ, C C No 72 004 669 de Barranquilla, para que en nombre y representaci n de la s ciedad firme las declaraci nes cambiarias a que este obligada PROCAPS S A a

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suscribir en el giro normal de sus negocios y operaciones sociales Por lo anterior, el senor ANTONIO VARELA DIAZ queda facultad para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones notificaciones aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado -

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2 005 bajo el No 2 820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C C 16 251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S A, otorga Poder Especial, Amplio y Suficiente al senor MARLON TATIS PAREDES C C No 72 176 874, para que en representacion de PROCAPS S A suscriba declaraciones aduaneras reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas naci - nales y/o cualquier entidad que haga sus veces y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las aut ridades aduaneras en los ordenes distrital, departamental y nacional ----------

C E R T I F I C A

Que por Escritura Publica No 1 613 del 28 de Junio del 2 005, otorgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 18 de agosto del 2 005 bajo el No 2 913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C C No 7 463 928, en su c ndicion de Presidente y Representante Legal de la sociedad PROCAPS S A confiere poder especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B para que c njuntamente suscriban contratos de suministro de mercancias y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US$800 000) liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion GRUPO A MIRIAM RODRIGUEZ DIAZ C C No 41 473 569 GRUPO B NELSON SUAREZ CHAVEZ, C C No 79 417 971 ------

C E R T I F I C A

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

C E R T I F I C A

Que su última Renovación fue el 29 de Marzo de 2006

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula la de contrat s sujetos a registro en Certificados Especiales

No 10544053

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ANEXO 1

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7
A61K 9/20, 47/26, 47/32

A1

(11) International Publication Number: WO 00/57857

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1999/10172 25 March 1999 (25.03.99) KR

(71) Applicant: YUHAN CORPORATION [KR/KR] 49-6 Taebang-dong, Tongjak-ku, Seoul 156-020 (KR).

(72) Inventors: KANG Dae, Sik; Yesulm Apt. #8-203 Sungpo-dong, Ansan-shi, Kyonggi-do 425-040 (KR). PARK Young, Joon Jugong Apt. #805-205 Burim-dong Kwachun-shi Kyonggi-do 427-050 (KR). KIM Hyun, Soo; Keukdong Baekdoo Apt. #968-403 Sanbon-dong, Kunpo-shi, Kyonggi-do 435-040 (KR).

(74) Agent: OH, Kook, Jin Yuhan Research Center 27-3, Tangjeong-dong, Kunpo-shi, Kyonggi-do 435-715 (KR).

(81) Designated States: AE, AG AL, AM, AT AU AZ, BA, BB BG, BR, BY CA, CH, CN CR, CU CZ, DE, DK, DM, DZ, EE, ES, FI GB GD, GE, GH, GM HR HU ID IL, IN IS JP KE, KG KP KZ, LC, LK, LR, LS, LT LU LV MA, MD MG MK MN MW MX, NO NZ, PL, PT RO RU SD, SE, SG SI, SK, SL, TJ TM, TR, TT TZ, UA UG, UZ, VN YU ZA, ZW ARIPO patent (GH, GM, KE, LS MW SD, SL, SZ, TZ, UG ZW), Eurasian patent (AM, AZ, BY KG KZ, MD RU TJ TM), European patent (AT BE, CH, CY DE, DK, ES, FI, FR, GB GR IE, IT LU MC, NL, PT SE), OAPI patent (BF BJ CF CG CI CM, GA GN GW ML, MR, NE, SN TD TG).

Published
With international search report
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments

(54) Title: RAPIDLY DISINTEGRABLE TABLET FOR ORAL ADMINISTRATION

(57) Abstract

The present invention relates to a rapidly disintegrable tablet for oral administration which disintegrates in the oral cavity within 60 seconds comprising (i) a therapeutically effective amount of an active ingredient, (ii) spray-dried mannitol (iii) crospovidone and (iv) one or more pharmaceutically acceptable excipients.

RAPIDLY DISINTEGRABLE TABLET FOR ORAL ADMINISTRATION

Field of the Invention

The present invention relates to a rapidly disintegrable tablet formulation of a drug, and more particularly, to a drug tablet for oral administration which disintegrates rapidly by the action of saliva in the oral cavity comprising (i) a therapeutically effective amount of an active ingredient, (ii) spray-dried mannitol as a disintegrant, (iii) crospovidone as a co-disintegrant, and (iv) one or more pharmaceutically acceptable excipients

Background of the Invention

It is not feasible to orally administer a conventional drug tablet to those having deglutition difficulties, or to patients whose water-intake must be restrictive Therefore, liquid type formulations are usually prescribed for those people, but liquid formulations have the problems of low storage stability handling difficulties and the inconvenience in measuring an accurate dose Accordingly there have been efforts to develop a rapidly disintegrable tablet formulation, which disintegrates rapidly and converts into a liquid form by the action of saliva in the oral cavity

U S Pat Nos 4,371,516 5,501 816 and 5,720,974 disclose processes for the preparation of porous rapidly disintegrable tablets which include the steps of adding a small quantity of a solvent to sugars alcohols or carbohydrates to obtain a tablet mixture and removing the solvent therefrom However these processes have low productivity due to the involvement of complicated process steps and the tablets obtained thereby are easily friable and do not meet the hardness required for withstanding breakage during commercial handling

U S Pat No 5 464,632 and European Pat Pub No 839 526 also disclose rapidly disintegrable tablets, which comprise one or more disintegrants including microcrystalline cellulose and swelling agents However, the water-insoluble microcrystalline cellulose remains undissolved in the oral cavity for some time, which often provides irritating sensation to patients

The present inventors have endeavored to develop an improved rapidly disintegrable tablets by solving the aforementioned problems and, have discovered that a tablet comprising spray-dried mannitol and crospovidone, a cross-linked poly(N-vinyl-2 pyrrolidinone) disintegrates rapidly in the oral cavity leaving no unpleasant water-insoluble residues, and has a hardness such that it is not friable during handling or shipment

Summary of the Invention

Accordingly, it is an object of the present invention to provide an improved rapidly disintegrable tablet for oral administration comprising a pharmacologically active ingredient, spray-dried mannitol and crospovidone

In accordance with the present invention, there is provided a tablet for oral administration, which disintegrates rapidly in the oral cavity within 60 seconds, comprising (i) a therapeutically effective amount of an active ingredient, (ii) spray-dried mannitol, (iii) crospovidone and (iv) one or more pharmaceutically acceptable excipients

Detailed Description of the Invention

As used herein, the term "therapeutically effective amount of an active ingredient refers to the amount which produces the desired therapeutic response upon oral administration and can be readily

determined by one skilled in the art In determining the therapeutically effective amount, a number of factors are considered, including but not limited to the particular compound administered, the bioavailability characteristics of the pharmaceutical composition administered, the dose regimen selected and other relevant factors

There is no limitation to the pharmacologically active ingredient to be used in the present invention Examples of the pharmacologically active ingredient, which may be used in the present invention are gastrointestinal function conditioning agents anti-inflammatory agents, analgesics agents for erectile dysfunction therapy anti-migraines, antihistaminic agents cardiovascular agents diuretics anti-hypertensive agents, anti-hypolipidemic agents, anti-ulcer agents anti-emetics, anti-asthmatic agents, anti-depressants, vitamins, anti-thrombotic agents, chemotherapeutic agents, hormones, anthelmintic agents and anti-diabetic agents

Representative examples of the above-mentioned gastrointestinal function conditioning agents include bromopride metoclopramide, cisapride and domperidone, the anti-inflammatory agents, aceclofenac diclofenac, flubiprofen, sulindac and celecoxib, the analgesics acetaminophen and aspirin, the agents for erectile dysfunction therapy, sildenafil and apomorphine, the anti-migraines, sumatriptan and ergotamin, the antihistaminic agents, loratadine, fexofenadine and cetirizine, the cardiovascular agents nitroglycerine and isosorbide dinitrate, the diuretics, furocemide and spironolactone, the anti-hypertensive agents, propranolol, amlodipine, felodipine, nifedipine captopril ramipril atenolol and diltiazem the anti-hypolipidemic agents, simvastatin, atrovastatin and pravastatin the anti-ulcer agents, cimetidine ranitidine famotidine, omeprazole and lansoprazol, the anti-emetics meclizine hydrochloride, ondansetron granisetron, ramosetron and tropisetron the anti-asthmatic agents, aminophylline theophylline terbutaline, fenoterol, formoterol and ketotifen, the anti-depressants,

fluoxetine and sertraline, the vitamins, Vit B1, B2, B6, B12 and C, the anti-thrombotic agents, sulfinpyrazone, dipyridamole and ticlopidine, the chemotherapeutic agents, cefaclor, bacampicillin, sulfamethoxazole and rifampicin, the hormones, dexamethasone and methyltestosterone, the anthelmintic agents, piperazine, ivermectine and mebendazole, and the anti-diabetic agents, acarbose, gliclazid and glipizid

Preferable active ingredients, which may be used in the present invention include acetaminophen domperidone, famotidine, meclizine hydrochloride, scopolamine hydrobromide, ondansetron cisapride granisetron, sildenafil, loratadine, and amlodipine

The spray-dried mannitol used as a primary disintegrant in the inventive tablet may be prepared by spray-drying an aqueous solution of crystalline mannitol and it has an average particle size of about from 10 to 200 μm A commercially available spray-dried mannitol powder (e g , PEARLITOL SD 200® Roquette, France) may also be used in the present invention

A spray-dried mannitol powder dissolves rapidly in an aqueous solution For example, at 20℃, a spray-dried mannitol powder dissolves in water at a rate that is 7 times faster than crystalline mannitol and 20 times faster than granular mannitol Also spray-dried mannitol dissolves in water faster than conventional white sugar white sugar for direct-compression, granular sorbitol and dextrate (a hydrolyzed starch) by factors of 10, 5-9, 7 and 3, respectively (see Test Example 1) In view of the fact that the water-solubilities of the above-mentioned saccharides are about 8 times higher than that of spray-dried mannitol the markedly high dissolution rate of spray-dried mannitol is remarkable

A spray-dried mannitol powder has improved flowability and compressibility than conventional crystalline mannitol, and thus, the tablet of the present invention may be obtained by a direct-compress process

Further, the improved compressibility of the spray-dried mannitol allows the hardness control of the resulting tablet through varying the compression pressure Also, the spray-dried mannitol is sweet (about 0 5 times than white sugar), pleasing to the taste of patients

The spray-dried mannitol is preferably used in an amount ranging from 30 to 95wt% based on the total weight of the inventive tablet

The tablet of the present invention further comprises crospovidone in an amount ranging from 1 to 10 wt% based on the total weight of the tablet as a secondary disintegrant, which enhances the dissolution (disintegration) rate of the spray-dried mannitol by way of bringing water in contact with the spray-dried mannitol through its capillary action

The tablet of the present invention may also contain one or more pharmaceutically acceptable excipients, including organic acids such as citric acid, tartaric acid, fumaric acid and malic acid, and effervescent agents such as calcium carbonate, sodium bicarbonate and potassium bicarbonate The organic acid and effervescent agent may be used in amounts ranging from 1 to 5 wt% based on the total weight of the tablet, respectively

The organic acids stimulate a salivary grand (parotid grand, sublingual grand and submaxillary gland) to facilitate saliva secretion, thereby accelerating the disintegration of the tablet, although the disintegration effect of organic acids per se is weak Further because the effervescent agent can react with water to give carbon dioxide, in case of using them in the tablet of the present invention, the effervescent agent react with saliva and/or organic acids in the oral cavity to give carbon dioxide, thus reducing the disintegration time of the inventive tablet.

Other pharmaceutically acceptable excipients may be also used in the present invention, including but not limited to sweetening agents such

as aspartam, saccharin, ammonium glycyrrhizinate xylitol, sorbitol and sucrose and lubricants such as colloidal silicon dioxide, magnesium stearate and magnesium trisilicate

The tablet of the present invention disintegrates rapidly in the oral cavity, leaving no significant amount of water-insoluble matter therein, and is not easily friable, as shown in the following Examples and Test Examples which are given for the purpose of illustration only, and are not intended to limit the scope of the invention

Example 1

12g of aspartam and 3g of colloidal silicon dioxide, each screened through a 20-mesh sieve were mixed and added thereto were 490 5g of spray-dried mannitol (Pearlitol SD 200®, Roquette) 18g of sodium bicarbonate and 18g of citric acid, each screened through a 40-mesh sieve This mixture was further mixed with 30g of crospovidone powder screened through a 20-mesh sieve, and then with 12g of magnesium trisilicate 4 5g of strawberry flavor and 12g of magnesium stearate, each screened through a 40-mesh sieve (see Table 1-1)

The resultant mixture was compressed into a tablet, using a single type tableting machine (Manesty F3, Manesty Machine Ltd), to provide a rapidly disintegrable tablet each weighing 600 mg

Example 2 - 6

The procedure of Example 1 was repeated using the components and active ingredients shown in Table 1-1 ~ 1-3 to obtain tablets according to the present invention

Table 1-1

(Unit gram)

		Ex.1	Ex 2	Ex 3	Ex 4	Ex 5	Ex 6
Active ingredients	Aacetaminophen	-	500 0	-	-	-	-
	Domperidone	-	10 0	-	-	-	-
	Famotidine	-	-	20 0	-	-	-
	Meclizine hydrochloride	-	-	-	25 0	-	-
	Scopolamine hydrobromide	-	-	-	0 1	-	-
	Ondansetron HCl	-	-	-	-	10 0	-
	Cisapride	-	-	-	-	-	10 0
Dis-integrants	Spray-dried mannitol	490 5	675 3	634 0	383 6	235 0	153 0
	Crospovidone	30 0	72 5	40 0	25 0	15 0	10 0
Organic Acids	Citric acid	18 0	43 5	24 0	15 0	9 0	6 0
Effervescent agents	Sodium bicarbonate	18 0	43 5	24 0	15 0	9 0	6 0
Sweetening agents	Aspartam	12 0	29 0	16 0	10 0	6 0	4 0
Flavors	Strawberry flavor	4 5	10 9	6 0	3 8	2 5	2 0
Lubricants	Colloidal silicon dioxide	3 0	7 3	4 0	2 5	1 5	1 0
	Magnesium trisilicate	12 0	29 0	16 0	10 0	6 0	4 0
	Magnesium stearate	12 0	29 0	16 0	10 0	6 0	4 0
Total weight		600	1 450	800	500	300	200
Pressure scale (gauge)		16 0	29 0	19 0	18 0	17 0	14 0
Diameter (mm)		12 5	18 0	14 0	12 0	10 0	9 5
Number of tablets		1,000	1,000	1,000	1,000	1 000	1 000

Table 1-2

(Unit gram)

		Ex 7	Ex 8	Ex 9	Ex 10
Active ingredients	Aacetaminophen	500 0	325 0	160 0	-
	Granisetron HCl	-	-	-	1 1
Dis-integrants	Spray-dried mannitol	320 0	405 0	404 0	150 0
	Crospovidone	94 0	94 0	72 0	16 0
Diluents	Xylitol	100 0	133 0	100 0	17 0
Organic Acids	Citric acid	21 0	21 0	16 0	4 0
Flavors	Herbal flavor	10 0	30 0	24 0	4 0
Sweetening agents	Aspartam	11 0	10 5	8 0	2 0
Lubricants	Magnesium trisilicate	22 0	21 0	8 0	4 0
	Magnesium stearate	22 0	10 5	8 0	1 9
Total weight		1,100	1,050	800	200
Pressure scale (gauge)		24 0	21 0	19 0	14 0
Diameter (mm)		16 0	16 0	14 0	9 5
Number of tablets		1,000	1,000	1,000	1 000

Table 1-3

(Unit gram)

		Ex 11	Ex 12	Ex 13
Active ingredients	Sildenafil	100 0	-	-
	Loratadine	-	10 0	-
	Amlodipine	-	-	5 0
Dis-integrants	Spray-dried mannitol	460 0	186 0	205 0
	Crospovidone	72 0	18 0	20 0
Diluents	Xylitol	100 0	25 0	-
Organic Acids	Citric acid	16 0	5 0	5 0
Flavors	Herbal flavor	20 0	6 0	5 0
Sweetening agents	Aspartam	8 0	2 5	2 5
Lubricants	Magnesium trisilicate	16 0	5 0	5 0
	Magnesium stearate	8 0	2 5	2 5
Total weight		800	260	250
Pressure scale (gauge)		20 0	17 0	17 0
Diameter (mm)		14 0	10 0	10 0
Number of tablets		1 000	1,000	1 000

Comparative Example 1-1, 1-2, 1-3 and 1-4

The procedure of Example 1 was repeated except that dextrate, white sugar A for direct compression, white sugar B for direct compression and sorbitol were each used in place of the spray-dried mannitol to obtain comparable tablets 1-1 1-2 1-3 and 1-4 respectively

Comparative Example 2-1, 2-2 and 2-3

The procedure of Example 2 was repeated except that cross-linked carboxymethyl cellulose sodium starch glycolate, and low substituted hydroxypropyl cellulose were each used in place of crospovidon to obtain comparable tablets 2-1, 2-2 and 2-3, respectively

Comparative Example 3-1~3-3, 4-1~4-3, 5-1~5-3 and 6-1~6-3

The procedures of Example 3 - 6 were repeated except that cross-linked carboxymethyl cellulose sodium starch glycolate and low substituted hydroxypropyl cellulose were each used in place of crospovidon to obtain respective comparable tablets

Test Method

The hardness and dissolution time in the oral cavity were measured by the following methods

(1) Hardness

The hardness of each tablet was measured with a tablet hardness tester (Schleuniger-2E, Dr K Schleuniger & Co) The test was repeated 3-10 times for each sample and the results were averaged

(2) Dissolution time

The time for a sample to completely disintegrate in the oral cavity of a male adult was measured The test was duplicated three times and the results were averaged

Test Example 1

5g of each of the test materials as shown in Table 2 was added to 150ml of purified water at 20℃ The time for the material to completely dissolve was measured and the results are shown in Table 2

Table 2

Compounds	Time (seconds)
Spray-dried mannitol (Pearlitol SD 200® Roquette)	5
Dextrate (Endex®, Edward Mendell)	16
White sugar for direct compression A (Sugartab®, Edward Mendell)	25
Crystalline mannitol	35
Sorbitol (Neosorb®, Roquette)	35
White sugar for direct compression B (Di-Pac® Domino Sugar Co)	45
White sugar	50
Xylitol (XYLISORB® Roquette)	74
Granular mannitol (Pearlitol 400 DC®, Roquette)	100

As can be shown in Table 2 the spray-dried mannitol dissolve more quickly than conventional sugar type excipients in an aqueous medium

Test Example 2

The hardnesses and disintegration time in the oral cavity were

measured for the tablets obtained in Example 1 and Comparative Examples 1-1 to 1-4 The results are shown in Table 3

Table 3

	Hardness (kp)	Disintegration Time (second)
Example 1	6 0	22 0
Comp Ex 1-1	6 1	42 3
Comp Ex 1-2	6 0	59 3
Comp Ex 1-3	6 1	51 7
Comp Ex 1-4	6 2	40 3

As can be seen in Table 3, the tablet obtained in Example 1, which contains spray-dried mannitol, disintegrates much faster than the comparable tablets containing conventional sugar type excipients

Test Example 3

The hardness and disintegration time in the oral cavity were measured for the tablets obtained in Examples and Comparative Examples shown in Table 4

Table 4

	Hardness (kp)	Disintegration Time (second)
Example 2	7 1	45 0
Comp Example 2-1	5 9	60 7
Comp Example 2-2	5 0	100 0
Comp Example 2-3	5 1	140 3
Example 3	6 1	35 3
Comp Example 3-1	5 4	54 7
Comp Example 3-2	4 9	70 0
Comp Example 3-3	4 8	97 3
Example 4	6 2	30 7
Comp Example 4-1	5 4	54 7
Comp Example 4-2	5 2	79 0
Comp Example 4-3	5 0	103 3
Example 5	5 1	30 0
Comp Example 5-1	4 5	50 7
Comp Example 5-2	4 3	70 3
Comp Example 5-3	4 6	95 0
Example 6	4 8	23 3
Comp Example 6-1	4 0	46 7
Comp Example 6-2	3 9	70 0
Comp Example 6-3	4 1	91 3

The results in Table 4 show that the inventive tablets show much shorter disintegration times and higher hardness values as compared with the tables of the corresponding Comparative Examples

Test Example 4

The hardness and disintegration time in the oral cavity were

measured for the tablets obtained in Example 7 ~ 13 shown in Table 5

Table 5

	Hardness (kp)	Disintegration Time (second)
Example 7	5 4	42 0
Example 8	4 5	40 3
Example 9	4 5	35 7
Example 10	4 1	20 7
Example 11	6 0	47 0
Example 12	4 0	32 0
Example 13	4 0	30 3

As can be seen in Table 5 the tablets of the present invention show disintegration times of less than 50 seconds

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made by those skilled in the art, which also fall within the scope of the invention as defined by the appended claims

What is claimed is

1 A tablet for oral administration, which disintegrates rapidly in the oral cavity within 60 seconds, comprising (i) a therapeutically effective amount of an active ingredient, (ii) spray-dried mannitol (iii) crospovidone and (iv) one or more pharmaceutically acceptable excipients

2 The tablet of claim 1, wherein the contents of the spray-dried mannitol and the crospovidone are in the ranges of 30 to 95% and 1 to 10% by weight, respectively, based on total weight of the tablet

3 The tablet of claim 1, wherein the active ingredient is selected from the group consisting of acetaminophen domperidone, famotidine meclizine hydrochloride, scopolamine hydrobromide, ondansetron cisapride, granisetron, sildenafil, loratadine and amlodipine

4 A process for the preparation of a tablet for oral administration which disintegrates rapidly in the oral cavity within 60 seconds, comprising direct-compressing a mixture containing (i) a therapeutically effective amount of an active ingredient, (ii) spray-dried mannitol, (iii) crospovidone and (iv) one or more pharmaceutically acceptable excipients

INTERNATIONAL SEARCH REPORT

International application No
PCT/KR 00/00242

A CLASSIFICATION OF SUBJECT MATTER

IPC[7] A 61 K 9/20 47/26, 47/32

According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7] A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ

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X	EP 0839526 A2 (TAKEDA CHEMICAL INDUSTRIES LTD) 06 May 1998 (06 05 98) abstract table 1 claims	1-4
Y	WO 87/01936 A1 (GERGELY) 09 April 1987 (09 04 87) abstract, claims	1-4
Y	GB 1504553 A (SANDOZ LTD) 22 March 1978 (22 03 78), page 1 column 1 lines 44-49 page 1 column 2 line 49	1-4

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex

* Special categories of cited documents
„A" document defining the general state of the art which is not considered to be of particular relevance
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„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 00/00242

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ANEXO 2

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(54) Title: NEW ORAL FORMULATION FOR 5-HT$_4$ AGONISTS OR ANTAGONISTS

(57) Abstract

The present invention relates to a pharmaceutical composition, in particular to a composition for administering active agents which are poorly soluble in aqueous media, and/or which are acid sensitive

NEW ORAL FORMULATION FOR 5-HT$_4$ AGONISTS OR ANTAGONISTS

The present invention relates to a pharmaceutical composition in particular to a composition for administering active agents which are poorly soluble in aqueous media and/or which are acid sensitive More particularly the present invention relates to a pharmaceutical composition for administering active agents acting on the gastro-intestinal system The present invention also relates to a process for manufacturing such compositions The term "pharmaceutical" also covers veterinary use

Pharmaceutical compositions containing active agents which are poorly soluble in aqueous media and/or acid sensitive are difficult to manufacture One of the problems that may occur concerns adsorption of the active agent on the process equipment during the manufacturing process Due to the poor solubility of such active agents it is also difficult to obtain pharmaceutical compositions which upon administration have a good dissolution rate As a further problem active agents may be degraded, e g chemically during a manufacturing process using acidic conditions or during the storage of the composition

The present invention provides compositions and processes which avoids or minimise one or more of the above problems

We have now surprisingly found that it is possible to produce a pharmaceutical composition for administering of active agents which are poorly soluble in aqueous media e g pure water and/or acid sensitive and which upon administration has good dissolution properties a good bioavailability and is surprisingly efficacious

The present invention provides in one aspect a solid oral pharmaceutical composition e g a tablet, comprising an active agent which is poorly soluble in aqueous media and/or acid sensitive and a disintegrant e g a super-disintegrant which is present in an amount of at least 15% by weight based on the total weight of the composition

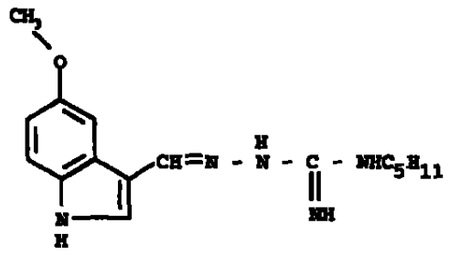
By "poorly soluble" is meant an active agent having a solubility in aqueous media more than 0 001% and less than 10% e g less than 1 % e g less than 0 1% e g less than 0 05%, e g less than 0 02% at room temperature e g 25°C

By "acid sensitive" is meant an active agent which under even slightly acidic conditions e g at pH 6 may be transformed to a significant extent in a degradation product e g by chemical degradation which may have no or changed activity e g within 2 hours Examples of compounds are known in the art and may be ascertained by routine experimentation

By "disintegrant" is meant a substance or mixture of substance added to a solid pharmaceutical composition e g a tablet to facilitate its break-up or disintegration after administration in order that the active ingredient is released from the composition as efficiently as possible to allow for its rapid dissolution (see e g "Remington s Pharmaceutical Science 18th edition (1990) "The Theory and Practice of Industrial Pharmacy" Lachman et al Lea & Febiger (1970))

We have also found difficulties on producing stable commercially acceptable formulations e g tablets of compounds such as those disclosed in EP505322 (herein incorporated by reference) and which are useful as 5-HT_4 receptor agonists or partial agonists

A preferred 5-HT_4 partial agonist disclosed in EP505322 is Tegaserod (3 (5-methoxy 1H-indol-3-yl methylene) N-pentylcarbazimidamide) (example 13) of formula



which is referred hereinafter as Compound A or a pharmaceutically acceptable salt form thereof e g the hydrogen maleate (hereinafter "hml") salt Compound A has a solubility of about 0 02% at 25°C in water and is acid sensitive We have found that compositions may be produced which give good absorption even in the stomach We have also found that Compound A may be adsorbed by certain excipients so that its dissolution upon administration may be substantially reduced

Little has been published in detail on 5 HT_4 receptor agonists, partial agonists or antagonists biopharmaceutical properties e g their site of action is not known

The present invention provides in a further aspect pharmaceutical compositions allowing a complete dissolution of 5-HT_4 receptor agonists partial agonists or antagonists e g Compound A when administered to humans, e g patients in need thereof These compositions allow a good bioavailability and are surprisingly efficacious Moreover they are stable and well reproducible A process for their preparation is also provided

Active agents which may be used in compositions according to the present invention are more generally those acting on the gastro-intestinal system e g serotonergic active agents e g full agonists partial agonists and antagonists of 5-HT_4 receptors to the extent they are poorly soluble and/or acid sensitive They are preferably in salt form e g hydrogen maleate or hydrochloride and may be in free form

The 5-HT_4 receptor is a cloned species of the serotonin receptor family which comprises at least 14 distinct G protein-coupled receptors (the receptor ionophore of the 5-HT_3 subtype excluded) Four splice variants of the human receptor 5-HT_{4A} 5 HT_{4B} 5-HT_{4C} and 5 HT_{4D} have been identified which differ in the length and sequence of the protein s C terminus (Blondel et al , FEBS Letters (1997) 412 465-474 Blondel et al. J Neurochem (1998) 70 2252 2261) Biochemical characterisation of 5-HT_4 receptors revealed a positive coupling to adenylyl cyclase 5-HT_4 receptor expression in man has been found in the brain the gut the atria the urinary bladder and kidneys

Compounds capable of acting on the serotonin receptor are substituted benzamides, *e g* cisapride renzapride zacopride clebopride cinitapride mosapride lintopride metoclopramide or benzoic esters *e g* RS 23597 190 SB 204070 SB 207710 or aminoguanidines zacopride prucalopride, SB 205149 SC 53116 RS 67333 RS 67506 BIMU 1 BIMU 8 (S)-RS 56532 Tropisetron Alosetron GR 113808 GR 125487 SB 207266 RS 23597, RS 39604 RS 100235 DAU 6285 SC 53606 3-(5-hydroxy-7 methyl-1H-indol-3-yl- methylene)-N-pentyl-N-methyl-carbazimidamide Indazole-3-carboxamides 2-oxobenzamidazole 3-carboxamides (as disclosed in EP 908 459 which is herein incorporated by reference) etc

5-HT_4 receptor agonists are considered as compounds which can activate 5-HT_4 receptors under quiescent/resting conditions (complete or partial activation) As 5 HT_4 receptor full agonists or partial agonists one may cite (S) zacopride cisapride prucalopride SB 205149 SC 53116 RS 67333 RS 67506 BIMU 1 BIMU 8 (S) RS 56532 and Compound A particularly its hydrogen maleate salt

5 HT_4 receptor antagonists are considered as compounds which do not activate 5-HT_4 receptors but act as inhibitors of agonists at 5 HT_4 receptors As 5-HT_4 receptor antagonists one may cite GR 113808 GR 125487 SB 203186 SB 204070 SB 207266 RS 23597 RS 39604 RS 100235 DAU 6285 SC 53606 3 (5 hydroxy 7-methyl-1H indol-3-yl-methylene) N-pentyl N methyl-carbazimidamide

5 HT_4 receptor agonists are useful for the prevention and treatment of gastro intestinal motility disorders e g Irritable Bowel Syndrome (IBS) Gastro-Esophageal Reflux Disease (GERD) Functional Dyspepsia (FD) and Post Operative Ileus (POI)

In a preferred embodiment the composition of the invention comprises 20 to 60% e g 30 to 50% e g 40% by weight of disintegrant based on the total weight of the composition We have observed that the use of such a high percentage of disintegrant further improves the dissolution rate in aqueous media but also prevents the active agent from adsorbing on excipients

As disintegrants the composition of the invention may comprise
- crospovidone (molecular weight $>10^6$) e g , Polyplasdone XL® Kollidon CL® , Polyplasdone XL 10®
  pregelatinised starch (MW 30 000 120 000) e g starch 1500® STA Rx 1500®
  sodium starch glycolate (MW 500 000 - 1 000 000) e g Primojel®
  carboxymethylcellulose calcium (CMC-Ca)
  carboxymethylcellulose sodium (CMC Na) (MW 90 000 700 000) e g Ac-Di-Sol®
  sodium alginate
or a mixture thereof

Preferably the disintegrant is crospovidone which is preferably water insoluble Preferably it rapidly exhibits high capillary or pronounced hydration capacity with little tendency to gel formation Preferably the particle size is from about 1 to 500 micrometers Preferred particle size distribution is less than 400 micrometers e g for Polyplasdone XL® less than 80 micrometers e g less than 74 micrometers for e g , Polyplasdone XL 10® approximately 50% greater than 50 micrometers and maximum of 1% greater than 250 micrometers in size for e g Kollidon CL® A preferred crospovidone is Polyplasdone XL® e g with a density of about 0 213 g/cm^3 (bulk) or 0 273 g/cm^3 (tapped)

The pharmaceutical composition of the invention may further comprise one or more excipients

The composition may further comprise one or more lubricants e g in an amount within the range of from e g 1 to 20% e g from 5 to 15% e g 10% by weight of the composition

Examples of such lubricants include
glyceryl mono fatty acid e g , having a molecular weight of from 200 to 800 e g glyceryl monostearate (e g Myvaplex® USP quality)
polyethylene glycol (PEG), having a molecular weight of from 100 to 10000 e g 1000 to 8000 e g 2000 to 6000 e g 2500 to 5000 e g Macrogol 4000 (Pulver) BP
hydrogenated castor oil (e g Cutina®) and the like
or a mixture thereof

In a preferred composition the lubricant is glyceryl monostearate The lubricant properties of such preferred composition may be improved by adding polyethylene glycol (PEG) e g Macrogol 4000 (Pulver) BP

The composition of the invention may comprise one or more surfactants e g in an amount in the range of from 0 1 to 10% e g 1 to 5% e g 2% by weight of the total composition Pharmaceutically suitable surfactants may be non-ionic or anionic

As non-ionic surfactants one may use
- polyoxyethylene-sorbitan-fatty acid esters (polysorbates, MW 500 to 2000) e g mono- and tri- lauryl palmityl stearyl and oleyl esters e g Tween® e g Tween 80®

polyoxyethylene fatty acid esters (MW 500 to 5000) e g , Myrj® or Cetiol®
polyoxyethylene-polyoxypropylene co-polymers e g having a molecular weight of from 1000 to 20 000 e g 6 000 to 15 000 e g 7 000 to 10 000 e g Pluronic® or Emkalyx®
polyoxyethylene polyoxypropylene block co-polymers e g having a molecular weight of from 1000 to 20 000 e g 6 000 to 15 000 e g 7 000 to 10 000, e g Poloxamer 188®
reaction products of a natural or hydrogenated castor oil and ethylene oxide e g Cremophor®
dioctylsuccinate or di-[2-ethylhexyl]- succinate
propyleneglycol mono- and di-fatty acid (e g C_6-C_8) esters e g Migiyol®
or mixtures thereof

As suitable anionic surfactants one may use e g sodium laurylsulfate or docusate sodium

Unless where otherwise stated fatty acid or carbon containing chain is from about 8 to 22 carbon atoms e g C_{16}

The composition of the invention may comprise one or more binders e g in an amount in the range of from 1 to 10% e g 2 to 8% e g 5% by weight. One may particularly use
hydroxypropylmethylcellulose e g having a molecular weight of from 10 000 to 1 500 000 e g HPMC-3 (3mPa-s) (e g Pharmacoat® Methocel®)
polyvinylpyrrolidone e g having a molecular weight of from 2500 to 3 000 000 e g 8 000 to 1 000 000 e g 10 000 to 400 000 e g 30 000 to 50 000 (e g Kollidon® Plasdone®)
potato starch wheat starch corn starch e g having a molecular weight of from 30 000 to 120 000
or a mixture thereof

The composition of the invention may comprise one or more diluents such as lactose mannitol sucrose calcium sulphate calcium phosphate microcristalline cellulose (Avicel®) in an amount within the range of from e g 10 to 70%, e g 20 to 50% e g 30% by weight of the composition Preferably the diluent is lactose e g lactose 200 mesh (e g from DMV® or Alpavit ®) e g the monohydrated form

Other conventional excipients which may optionally be present in the composition of the invention include preservatives stabilisers anti-adherents or silica flow conditioners or glidants e g , silicon dioxide (e g Syloid® Aerosil®) as well as FD&C colours such as ferric oxides.

Other excipients disclosed in the literature as for instance in Fiedler's "Lexicon der Hilfstoffe 4th Edition ECV Aulendorf 1996 and "Handbook of Pharmaceutical Excipients" Wade and Weller Ed (1994) the contents of which are incorporated herein by reference may be used in the pharmaceutical compositions according to the invention

The invention is particularly useful for pharmaceutical compositions containing an active agent e g an $5HT_4$ receptor agonist partial agonist or antagonist e g compound A e g the hydrogen maleate salt which is present in an amount within the range of from about 0.2% to about 20% e g 0 5 to 15% and preferably from about 1% to about 10% by weight of the composition

A preferred composition of the invention may comprise from about 0 5 to about 15% by weight of active agent e g a $5HT_4$ receptor agonist e g compound A e g the hydrogen maleate salt from 20 to 60% by weight of disintegrant e g crospovidone from 1 to about 20% by weight of a lubricant, e g monoglycerylstearate from 0 1 to about 10% by weight of a surfactant, e g poloxalkol from about 10 to 50% by weight of a diluent e g lactose and from 1 to 10% by weight of a binder e g hydroxypropylmethyl cellulose (e g HPMC-3) From 1 to 10% by weight of PEG may also be added

The weight ratio of the active agent to the disintegrant may be from 1 1 to 1 400 e g 1 5 to 1 100 1 8 to 1 50 e g , 1 16 to 1.20

In a further aspect the present invention provides a pharmaceutical oral e g tablet, composition comprising one of the active agents cited above e g a 5 HT_4 agonist partial agonist or antagonist, e g Tegaserod said composition having dissolution characteristics in water or in USP buffers pH 6 8 and 7 5 of

time (minutes)	amount (percentage)
5	30 – 90

15	80 100
30	95 100
60	100

For example a composition according to the invention e g comprising Tegaserod as the active agent, may have dissolution characteristics in water or in USP buffers pH 6 8 and 7.5 of

time (minutes)	amount (percentage)
5	48 9
15	95 5
30	99 7
60	100

In a further aspect the present invention provides a pharmaceutical oral e g tablet, composition comprising one of the active agents cited above e g a 5-HT_4 agonist partial agonist or antagonist, e g Tegaserod wherein in use 80% of said active agent is released in water or in USP buffers pH 6 8 and 7 5 within 5 minutes

In a further aspect, the present invention provides the use of at least 15% by weight of a disintegrant in the manufacturing of pharmaceutical composition for the administration of an acid sensitive and/or poorly soluble e g in aqueous media, active agent e g a 5 HT_4 receptor agonist, e g compound A, e g the hydrogen maleate salt.

The pharmaceutical compositions of the present invention are useful in the known indications of the particular active agent incorporated therein

The exact amounts of active agent and of the formulation to be administered depend on a number of factors, e g the condition to be treated the desired duration of treatment and the rate of release of active agent.

For example the amount of the active agent required and the release rate thereof may be determined on the basis of conventional in vitro or in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

Examples of doses provided in a solid formulation e g a tablet, are for Irritable Bowel Syndrome (IBS), 1 mg to 12 mg of active agent for functional dyspepsia (FD) and gastroesophageal reflux disease (GERD) 0.2 to 2mg of active agent in particular compound A, e g the hydrogen maleate salt per day for a 70 kilogram mammal e g humans and in standard animal models The increased tolerability of the active agent in particular compound A e g the hydrogen maleate salt provided by the compositions may be observed in standard animal tests and in clinical trials

The pharmaceutical composition of the invention comprising a 5 HT_4 receptor agonist partial agonist or antagonist is particularly useful for improving sensory perception of rectal distension e g for the treatment of anal incontinence or for preventing modulating or treating visceral pain or discomfort.

5 HT_4 receptor agonists partial agonists or antagonists e g as disclosed in EP A1 505 322 on the basis of observed activity e g stimulatory effect on the peristaltic reflex in the isolated guinea-pig ileum e g as described in EP A1-505 322 have been found to be useful for the treatment of gastro-intestinal motility disorders for example to normalise or to improve the gastric emptying and intestinal transit in subjects having a disturbed motility e g in irritable bowel syndrome

In accordance with the present invention it has now surprisingly been found that 5-HT_4 receptor agonists, partial agonists or antagonists have a beneficial effect e g they exert modulating effects on the sensory perception of rectal distension and on visceral sensitivity or perception

It is admitted that receptor properties are not uniform throughout the gut and that the type of afferent innervation reflects the quality of sensations originating from a particular organ For example the rectum belongs to those parts of the gastro-intestinal tract from which also non-painful sensations arise In contrast to the colon from which only painful sensations emanate

Anal incontinence may be due to functional disturbances of the main anal continence mechanisms Anal continence appears to be based on a co-ordinated functioning of the

neuromuscular machinery managing rectal sensation and compliance, the recto-anal inhibitory reflex reflex contractions of the external anal sphincter and the puborectalis muscle Although skeletal muscle (external sphincter and puborectalis) contractions are of great importance in the maintenance of continence it is probably the triggering effect of rectal sensation and perception that plays a crucial role and in fact, is frequently abnormal in incontinent patients Anal incontinence is a dysfunction which occurs particularly in diabetics and the elderly population

There is a medical need for modulating visceral sensitivity discomfort or pain in patients suffering from gastro-intestinal disorders and for a treatment of anal continence dysfunctions

In accordance with the particular findings of the present invention there is provided

1 1 A method for preventing modulating or treating visceral e g abdominal pain or discomfort in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT_4 receptor agonist partial agonist or antagonist or a pharmaceutically acceptable salt thereof

1 2 A method for modulating visceral sensitivity or perception in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT_4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof

1 3 A method for stimulating 5-HT_4 receptors present on afferent nerve terminals, particularly on extrinsic neurones of the gut, in a subject in need thereof which method comprises administering to said subject an effective amount of a 5-HT_4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof

1 4 A method for modulating visceral sensitivity discomfort or pain via stimulation of 5-HT_4 receptors present on afferent nerve terminals particularly on extrinsic neurones of the gut, in a subject in need thereof which method comprises administering to said subject an effective amount of a 5-HT_4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof

1 5 A method for regulating or stabilising myenteric plexus-afferent fibbers in a subject in need thereof which method comprises administering to said subject an effective amount of a 5-HT_4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof

1 6 A method for improving sensory perception of rectal distension in a subject in need thereof which method comprises administering to said subject an effective amount of a 5-HT_4 receptor agonist partial agonist or antagonist or a pharmaceutically acceptable salt thereof

1 7 A method for treating anal continence dysfunctions in a subject in need thereof which method comprises administering to said subject an effective amount of 5-HT_4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof

As alternative to the above the present invention also provides

2 A 5 HT_4 receptor agonist partial agonist or antagonist or a pharmaceutically acceptable salt thereof for use in a method as defined under 1 1 to 1 7 above or

3 A 5-HT_4 receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof for use in the manufacture of a pharmaceutical composition for use in a method as defined under 1 1 to 1 7 above or

4 A pharmaceutical composition for use in a method as defined under 1 1 to 1 7 above comprising a 5-HT_4 receptor agonist partial agonist or antagonist or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable diluents or carriers therefor e g a composition such as disclosed hereinabove

Preferred compounds for use in accordance with the invention include e g those listed hereinabove, particularly 5 HT_4 receptor full agonists or partial agonists e g (S) zacopride cisapride prucalopride SB 205149 SC 53116 RS 67333 RS 67506 BIMU 1 BIMU 8 (S)-RS 56532 especially Compound A and particularly its hydrogen maleate salt more

preferably selective 5 HT_4 receptor agonists or partial agonists, and 5-HT_4 receptor antagonists, e g Tropisetron, GR 113808, GR 125487 SB 204070 SB 207266 RS 23597 RS 39604 RS 100235 DAU 6285 SC 53606 3-(5-hydroxy 7-methyl-1H-indol-3-yl methylene) N-pentyl-N-methyl-carbazimidamide etc By selective is meant a compound which does not substantially bind to or stimulate the serotonin 5-HT_3 receptor A group of compounds excludes Tropisetron

Utility of a 5 HT_4 receptor agonist, partial agonist or antagonist in the prevention modulation or treatment of visceral *e g* abdominal pain or discomfort or modulation of visceral sensitivity or perception or regulation or stabilisation of myenteric plexus afferent fibers is demonstrated in convenient tests e g in accordance with the method hereinafter described

Decerebrate anaesthesia free cats under continuous monitoring of blood pressure are paralysed by alcuronium chloride dissolved in rheomacrodex i v (200 µg/kg initially and supplementary doses of 100 µg/kg if necessary), and artificially ventilated Single unit activity of afferent fibres are recorded in a monopolar fashion from peripheral endings of centrally cut filaments of sacral dorsal roots Tension receptors are identified by probing of their receptive fields in the wall of the mobilised rectum. Thereafter the response of the units to barostat -controlled rectal ramp-distension is determined The quantitative response characteristics of the units is evaluated with respect to distension pressure and resulting rectal diameter Alternatively the response of the units to pressure-induced peristalsis is measured

After obtaining 2 distension profiles (5 min each) and/or 10 min of peristalsis under control conditions a 5-HT_4 receptor agonist partial agonist or antagonist *e g* Compound A or vehicle is applied i v and the protocol is repeated Subsequently the activity of additional units is recorded in the presence of a 5-HT_4 receptor agonist partial agonist or antagonist, *e g* Compound A or vehicle according to the distension/peristalsis protocol In this assay the firing rate of the rectal afferents is reduced after administration of a 5-HT_4 receptor agonist or partial agonist at a dose range of from 0 1 to 3 mg/kg i v , at distension pressures above 20 mmHg With Compound A administered i v in incremental doses from 0 15 to 1 2

mg/kg the most prominent inhibition occurs at 50 mmHg and a half-maximal reduction is obtained at about 0 7 mg/kg

Utility of a 5 HT_4 receptor agonist partial agonist or antagonist, *e g* Compound A in the treatment of anal incontinence as well as utility in treating conditions as hereinabove specified may be demonstrated in accordance with the method hereinafter described

Intraluminal pressures and reflexes in the last 60 cm of the colon of 10 fasted healthy volunteers are measured by means of perfusion manometry Three latex balloons positioned at 50 30 and 10 cm allow volume stimulation Basal values of colonic intraluminal pressures and reflexes are established Subsequently reflex inhibitory relaxations of the internal anal sphincter is triggered by inflating the balloons by 10 ml increments up to a maximum volume of 150 ml During the inflation phase two parameters are evaluated a) the reflux threshold (volume able to induce a substantial pressure decrease of the internal anal sphincter) and b) the sensation threshold (volume able to induce a conscious defecation reflex) After the basal recordings each subject is given a 5-HT_4 receptor agonist partial agonist or antagonist, *e g* Compound A, p o and 30 to 90 min later the colonic intraluminal pressure and reflexes are assessed again by the same method In this test, the 5-HT_4 receptor agonist partial agonist or antagonist *e g* Compound A significantly reduced the sensation threshold when administered at a dose of 2 12 mg p o

5 HT_4 receptor agonists partial agonists or antagonists *e g* Compound A may be administered by any conventional route in particular enterally preferably orally *e g* in the form of tablets or capsules, or parenterally *e g* in the form of injectable solutions or suspensions or in a suppository form

5-HT_4 receptor agonists partial agonists or antagonists *e g* Compound A, may be administered in free form or in pharmaceutically salt form Such salts exhibit the same order of activity as the 5 HT_4 receptor agonists partial agonists or antagonists in free form

Daily dosages required in practising the method of the present invention will vary depending upon for example the particular compound employed the mode of administration and the

severity of the condition to be treated An indicated daily dose is in the range of from about 0 05 to about 30 mg *e g* from about 0 05 to about 5 mg for parenteral use and of from about 0 1 to about 30 mg for oral use conveniently administered once or in divided dosages 2 to 4x/day or in sustained release form Unit dosage forms for oral administration accordingly comprise from about 0.5 to about 30 mg of 5-HT_4 receptor agonist partial agonist or antagonist, *e g* Compound A or a pharmaceutically acceptable salt thereof admixed with an appropriate solid or liquid pharmaceutically acceptable diluent or carrier therefor

Furthermore it has also been found that a 5-HT_4 receptor agonist or partial agonist-*e g* Compound A have a beneficial effect in the prevention or treatment of gastro-intestinal motility disorders e g a stimulatory effect on gastrointestinal motility in horses and cattle

Accordingly, there is also provided

5 1 A method for preventing or treating gastro-intestinal motility disorders e g by stimulating the motility of the gastro-intestinal tract in horses or cattle in need thereof which method comprises administering to the horses or cattle an effective amount of a 5-HT_4 receptor agonist or partial agonist, *e g* Compound A or a pharmaceutically acceptable salt thereof

5 2 A method for preventing or treating gastro-intestinal motility disorders e g after colic surgery e g post-operative ileus in horses or cattle in need thereof which method comprises administering to the horses or cattle an effective amount of a 5 HT_4 receptor agonist or partial agonist, *e g* Compound A or a pharmaceutically acceptable salt thereof

6 A 5-HT_4 receptor agonist or partial agonist *e g* Compound A or a pharmaceutically acceptable salt thereof for use as a veterinary pharmaceutical e g for horses or cattle e g in any of the method 5 1 or 5 1 indicated above or for use in the manufacture of a veterinary pharmaceutical e g. for use in a method as defined under 5 1 or 5.2

7 A pharmaceutical composition for veterinary use, e g in horses or cattle e g in any of the method 5 1 or 5.2 as indicated above comprising a 5-HT_4 receptor agonist or partial agonist *e g* Compound A or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier therefor e g a composition as disclosed hereinabove

Preferred 5-HT_4 receptor agonists or partial agonists for use in horses or cattle in accordance with the invention include e g those listed hereinabove e g (S) zacopride prucalopride SB 205149 SC 53116 RS 67333 RS 67506 BIMU 1 BIMU 8 (S)-RS 56532 especially Compound A and particularly its hydrogen maleate salt more preferably a selective 5 HT_4 receptor agonist or partial agonist.

Utility of a 5-HT_4 receptor agonist or partial agonist *e g* Compound A in the treatment of post-operative ileus as well as utility in treating conditions as hereinabove specified in horses or cattle may be demonstrated in accordance with the method hereinafter described

20 horses having colic syndrome are submitted to abdominal surgery During surgery supportive therapy is applied to them At the end of surgery a specific 5 HT_4 receptor agonist or partial agonist *e g* Compound A is administered i v or i m e g at a dose of from 0 01 to 10 mg/kg This dose is repeated every 8 to 24 h until spontaneous defecation is observed Gastro-intestinal motility is evaluated based e g on the presence or absence of gastric reflux as determined by nasogastric intubation occurrence of borborygmi and timing of defecation after the first injection of the test compound In this test, the compounds tested *e g* Compound A, are effective in restoring normal motility function of the equine intestine

Daily dosages required in practising the veterinary method of the present invention will vary depending upon for example the particular compound employed the mode of administration and the severity of the condition to be treated An indicated daily dose is in the range of from about 0 01 to about 10 mg/kg *e g* from about 0 05 to about 5 mg/kg for parenteral use conveniently administered once or in divided dosages 2 to 4x/day or in sustained release form

In a further aspect the invention provides a method for preventing or treating gastro-intestinal motility disorders in a subject e g , a human or an animal in need of such a therapy comprising administering to this subject an effective amount of a composition according to the present invention

In a further aspect the invention a process is provided for improving dissolution properties in aqueous media of a pharmaceutical composition containing an acid sensitive and/or poorly soluble in aqueous media active agent e g a 5-HT_4 receptor agonist, more particularly compound A e g the hydrogen maleate salt

The pharmaceutical composition of the invention may be prepared by any conventional method known in the art e g by mixing an appropriate amount of the active agent e g a 5 HT_4 receptor agonist with at least 15% e g from 20 to 60%, e g from 30 to 50% e g 40% by weight of a disintegrant based on the total weight of the composition

It is preferred to formulate in solid form e g unit dosage form Typical form include capsules and preferably compressed forms such as tablets.

The pharmaceutical composition according to the invention may be prepared by e g a wet, e g water based granulation manufacturing process (the process equipment, as glass material may be pre-treated with a siliconizing agent) comprising the successive steps of

i) pre-mixing the acid sensitive and/or poorly soluble in water active agent e g a 5-HT_4 receptor agonist e g compound A, e g the hydrogen maleate salt with 60 to 98% of the diluent, and then sieving the resulting mixture

ii) mixing purified water with the binder in a weight ratio of from 1 20 to 3 20 and stirring until dissolution

iii) adding the surfactant to the solution of ii) and stirring until dissolution

iv) adding the disintegrant the remaining diluent and 50 to 70% of the first lubricant to the pre mixture of i) and mixing

v) wetting the mixture of step iv) with the granulating solution from step iii) while mixing

vi) granulating the mixture of step v) by mixing

vii) drying the granulate to reach a required loss on drying e g for the tabletting mixture

viii) sizing the granulate by sieving

For tablet manufacturing the granulate from viii) is mixed e g in a free fall mixer with the rest of the first lubricant and the second one to obtain the desired final tabletting mixture which may be compressed into tablets This may be performed with conventional tabletting machines on e g a rotary machine at compression pressures of, e g 2 to 30 KN e g 5 to 27 KN e g 10 to 20 KN (KN = Kilo Newtons)

The composition according to the invention may also be prepared by an alternative wet granulation manufacturing process wherein the pre-mixing and sieving of step i) are not performed In this case, the active agent, the disintegrant the diluent and about 60% of the first lubricant are pre-blended together and then wetted with the wetting solution of step iv)

Compositions comprising any of the above-mentioned active agents may be prepared by a process as disclosed above

If desired the pharmaceutical compositions of the invention are stored under low relative humidity conditions e g rH (relative humidity) less than 50% e g below e g 30-50% and at room temperature, preferably less than 20°C The compositions provide storage stable systems. Insignificant degradation is detected after storage of up to 1 year at room temperature e g 25 °C

The compositions of the invention may be packed in conventional manner to keep out humidity e g , in a blister pack optionally with a desiccant.

The compositions of the invention may have a water content of from 0 to 3% based on the total weight of the composition

The present invention relates in a further aspect to a composition in particular comprising compound A as obtained by one of the above processes to provide a small stable form

Examples

The following examples illustrate the manufacturing on an industrial scale, of compositions comprising compound A hml using a wet granulation process as disclosed above

Example 1

A 2 mg tablet formulation may be prepared as described hereinafter

a) Preparation of the granulated material

Premixing step

1 4 432 kg of compound A hml and 28 688 kg of lactose monohydrate are mixed with an intensive mixer (Colette Gral® 300 l or Fielder®) mixer speed setting 1 chopper speed setting 1) for approximately 1 5 minutes or with a free fall mixer (Turbula® Soneco® or Röhnrad®)

2 The pre mixture from step 1 is then sieved (oscillating granulator e g , Frewitt® or Erweka®· mesh size 0 8 millimetres)

3 The pre-mixture is divided into two portions of 16.560 kg

Preparation of the granulating solution

4 Approximately 40 kg of purified water are weighed out

5 3 600 kg of methylhydroxypropylcellulose 3 maps are added to the purified water from step 4 and this is stirred until dissolution

6 1 440 kg of poloxamer 188 are added to the solution from step 5 while stirring until dissolution

Granulating step

7 28.800 kg of crospovidone 10 080 kg of lactose monohydrate and 4 320 kg of glyceryl monostearate are weighed out

8 One portion of the premixture from step 3 is added to the excipients from step 7 and this is mixed with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 1) for approximately 2 minutes

9 The mixture from step 8 is wetted with the granulating solution from step 6 while mixing with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed

setting 1 chopper speed setting 0 pumping rate approximately 4 kg/minute) for approximately 12 minutes

10 Approximately 2 kg of purified water are weighed out.

11 The vessel from step 6 is rinsed with the purified water from step 10 and this is added to the mixture from step 9 while mixing

12 The mass is granulated by mixing with the intensive mixer Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 1) for approximately 2.5 minutes

Drying step

13 The granulate from step 12 is dried in a fluidised air bed drier (e g Glatt® or Aeromatic®) for approximately 65 minutes (inlet air temperature approximately 70°C) to reach the required loss on drying (LOD) for the tabletting mixture i e until LOD ≤4 4%

14 The granulate sized by sieving (0 8 millimetres) with an oscillating sieve granulator e g Frewitt® or Erweka®

15 Steps 4 to 14 are repeated with the other portion of step 3

b) Preparation of the tabletting mixture

16 8 640 kg of polyethylene glycol 4000 and 5 760 kg of glyceryl monostearate are sieved (oscillating granulator e g , Frewitt® or Erweka® mesh size 0 8 millimetres)

17 The ingredients from step 16 are added to the total mass of granulated material and this is mixed with a free fall mixer e g Soneco® or Röhnrad® for approximately 20 minutes (10 rpm) to obtain the desired final tabletting mixture

c) Compression step

18 The tabletting mixture from step 17 is pressed into tablets using compression pressures of 11 14 or 17 KN on a rotary tabletting machine e g Fette® Korsh® Kellan® or Coarty® (temperature < 20°C rH (relative humidity) < 40%)

Example 2 . Composition of a 2 mg tablet (1 mg of base corresponds to 1,385 mg of the hydrogen maleate salt of compound A)

Compound A hml	2 77 (2mg base)
Polyplasdone XL USP/NF	36 00
Glyceryl monostearate USP/NF	9 00
Poloxalkol	1 80
Lactose 200 mesh	30 53
HPMC 3cPs	4 50
Polyethyleneglycol 4000	5 40
Water adsorbed	2 00
Total	92 mg

Example 3

A 6 mg tablet formulation may be prepared by the manufacturing process described hereinafter

a) Preparation of the granulated material

Preparation of the granulating solution

1 Approximately 40 kg of purified water are weighed out

2 3 600 kg of methylhydroxypropylcellulose 3 maps are added to the purified water from step 1 while stirring until dissolution

3 1 440 kg of poloxamer 188 are added to the solution from step 2 while stirring until dissolution (mixing tank under stirring)

Granulating step

4 4 787 kg of compound A hml and 28 800 kg of crospovidone 21 853 kg of lactose monohydrate and 4 320 kg of glyceryl monostearate are weighed out

5 The ingredients from step 4 are mixed with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 1) for approximately 2 minutes

6 The mixture from step 5 is wetted with the granulating solution from step 3 while mixing with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed

setting 1 chopper speed setting 0 pumping rate approximately 4 kg/minute) for approximately 12 minutes

7 Approximately 2 kg of purified water are weighed out

8 The vessel from step 3 is rinsed with the purified water from step 7 and this is added to the mixture from step 6 while mixing

9 The mass is granulated by mixing with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 1) for approximately 2 5 minutes

Drying step

10 The granulate from step 9 is dried in a fluidised air bed drier e g Glatt® or Aeromatic®) for approximately 65 minutes (inlet air temperature approximately 70 C) to reach the desired loss on drying (LOD) for the tabletting mixture i e until LOD ≤4 4%

11 The granulate sized by sieving (0 8 millimetres) with an oscillating sieve granulator (Frewitt® or Erweka®)

12 Steps 1 to 11 are repeated

b) Preparation of the tabletting mixture

13 8 640 kg of polyethylene glycol 4000 and 5 760 kg of glyceryl monostearate are sieved with an oscillating sieve granulator e g , Frewitt® or Erweka® (0.8 millimetres)

14 The ingredients from step 13 are added to the total mass of granulated material and this is mixed with a free fall mixer e g Soneco® or Röhnrad® for approximately 20 minutes (10 rpm) in the desired final tabletting mixture

c) Compression step

15 The tabletting mixture from step 14 is pressed into tablets using compression pressures of 13 16 or 19 KN on a rotary tabletting machine e g Fette® Korsh® Kellan® or Coarty® (temperature<20°C rH (relative humidity) < 40 %)

Example 4 . Composition of a 6 mg tablet (1 mg of base corresponds to 1.385 mg of hydrogen maleate of compound A).

Compound A hml	8 31 (6mg base)
Polyplasdone XL USP/NF	50 00
Glyceryl monostearate USP/NF	12 50
Poloxalkol	2 50
Lactose 200 mesh	37 94
HPMC 3cPs	6 25
Polyethyleneglycol 4000	7.50
Water adsorbed	3 00
Total	128 mg

Example 5

A 0 5 mg tablet formulation may be prepared by the manufacturing process described hereinafter

a) Preparation of the granulated material

Premixing step

1 1 994 kg of compound A hml and 31 126 kg of lactose monohydrate are mixed with an intensive mixer (Colette Gral® 300 l or Fielder®) mixer speed setting 1 chopper speed setting 1) for approximately 1 5 minutes or with a free fall mixer (Turbula® Soneco® or Röhnrad®)

2 The premixture from step 1 is then sieved (oscillating granulator e g Frewitt® or Erweka® mesh size 0 8 millimetres)

3 The premixture is divided into two portions of 16 560 kg

Preparation of the granulating solution

4 Approximately 43 kg of purified water are weighed out.

5 3 600 kg of methylhydroxypropylcellulose 3 maps are added to the purified water from step 4 and this is stirred until dissolution

6 1 440 kg of poloxamer 188 are added to the solution from step 5 while stirring until dissolution

Granulating step

7 28 800 kg of crospovidone, 10 080 kg of lactose monohydrate and 4 320 kg of glyceryl monostearate are weighed out.

8 One portion of the premixture from step 3 is added to the excipients from step 7 and this is mixed with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 1) for approximately 2 minutes

9 The mixture from step 8 is wetted with the granulating solution from step 6 while mixing with the intensive mixer e g Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 0 pumping rate approximately 4 kg/minute) for approximately 12 minutes

10 Approximately 2 kg of purified water are weighed out

11 The vessel from step 6 is rinsed with the purified water from step 10 and this is added to the mixture from step 9 while mixing

12 The mass is granulated by mixing with the intensive mixer Colette Gral® 300 l or Fielder® (mixer speed setting 1 chopper speed setting 1) for approximately 2 5 minutes

Drying step

13 The granulate from step 12 is dried in a fluidised air bed drier (e g Glatt® or Aeromatic®) for approximately 60 minutes (inlet air temperature approximately 70°C) to reach the required loss on drying (LOD) for the tabletting mixture i e until LOD ≤4 5%

14 The granulate sized by sieving (0 8 millimetres) with an oscillating sieve granulator e g , Frewitt® or Erweka®

15 Steps 4 to 14 are repeated with the other portion of step 3

b) Preparation of the tabletting mixture

16 6 640 kg of polyethylene glycol 4000 and 5 760 kg of glyceryl monostearate are sieved (oscillating granulator e g Frewitt® or Erweka® mesh size 0 8 millimetres)

17 The ingredients from step 16 are added to the total mass of granulated material and this is mixed with a free fall mixer, e g Soneco® or Röhnrad® for approximately 20 minutes (10 rpm) to obtain the desired final tabletting mixture

c) Compression step

18 The tabletting mixture from step 17 is pressed into tablets on a rotary tabletting machine e g Fette® Korsh® Kellan® or Coarty® (temperature < 20°C rH (relative humidity) < 40%)

Example 6 . Composition of a 0,5 mg tablet (1 mg of base corresponds to 1,385 mg of the hydrogen maleate salt of compound A)

Compound A hml	0 6925 (0 5mg base)
Polyplasdone XL USP/NF	20 00
Glyceryl monostearate USP/NF	5 00
Poloxalkol	1 00
Lactose 200 mesh	17 8075
HPMC 3cPs	2.50
Polyethyleneglycol 4000	3 00
Water adsorbed	1 00
Total	51 mg

Example 7 . Composition of a 12 mg tablet (1 mg of base corresponds to 1,385 mg of the hydrogen maleate salt of compound A)

The manufacturing process is similar to the process used for the 6mg tablets

Compound A hml	16 62 (12mg base)
Polyplasdone XL USP/NF	72 00
Glyceryl monostearate USP/NF	18 00
Poloxalkol	3 60
Lactose 200 mesh	49 98
HPMC 3cPs	9 0
Polyethyleneglycol 4000	10 8
Water adsorbed	4 00
Total	184 mg

Claims

1 A solid oral pharmaceutical composition comprising an effective amount of an acid sensitive active agent and a disintegrant which is present in an amount of at least 15% by weight based on the total weight of the composition

2 A solid oral pharmaceutical composition comprising an effective amount of an active agent which is poorly soluble in aqueous media and a disintegrant which is present in an amount of at least 15% by weight based on the total weight of the composition

3 A pharmaceutical composition according to claim 1 or 2 wherein the active agent has a solubility in aqueous media less than 1%.

4 A pharmaceutical composition according to any of claims 1 to 3 wherein the active agent is a serotonergic compound

5 A pharmaceutical composition as claimed in any preceding claim wherein the active agent is a 5-HT_4 receptor antagonist

6 A pharmaceutical composition as claimed in any of claims 1 to 4 wherein the active agent is a 5-HT_4 receptor agonist.

7 A pharmaceutical composition according to claim 6 wherein the 5 HT_4 receptor agonist is Tegaserod preferably its hydrogen maleate (hml) salt

8 A pharmaceutical composition as claimed in any preceding claim wherein the disintegrant is crospovidone

9 A pharmaceutical composition as claimed in any preceding claim comprising a lubricant.

10 A pharmaceutical composition according to claim 9 wherein the lubricant comprises a glyceryl mono fatty acid

11 A pharmaceutical composition according to claim 9 wherein the lubricant comprises a mixture of glyceryl monostearate and polyethylene glycol

12 A pharmaceutical composition as claimed in any preceding claim comprising a surfactant.

13 A pharmaceutical composition according to claim 12 wherein the surfactant comprises poloxamer

14 Use of at least 15% by weight of a disintegrant in the manufacturing of a solid pharmaceutical composition for the administering of an acid sensitive active agent.

15 Use of at least 15% by weight of a disintegrant in the manufacturing of a solid pharmaceutical composition for the administering of an active agent being acid sensitive and/or having a poor water solubility

16 Use according to claim 14 or 15 wherein the active agent is a 5-HT_4 receptor agonist.

17 Use according to claim 16 wherein the 5-HT_4 receptor agonist is Tegaserod preferably its hydrogen maleate salt.

18 Use of a pharmaceutical composition according to any one of claims 1 to 13 for the the manufacture of a composition for the prevention and treatment of gastro-intestinal motility disorders in humans or animals

19 A process for improving dissolution properties of a pharmaceutical composition as claimed in any of claims 1 to 13

20 A method for preventing modulating or treating visceral pain or discomfort, for modulating visceral sensitivity or perception for improving sensory perception of rectal distension or for treating anal continence dysfunctions in a subject in need thereof, which method comprises administering to said subject an effective amount of a 5-HT_4

receptor agonist, partial agonist or antagonist or a pharmaceutically acceptable salt thereof

21 A 5-HT_4 receptor agonist partial agonist or antagonist or a pharmaceutically acceptable salt thereof for use in the manufacture of a pharmaceutical composition for use in preventing modulating or treating visceral pain or discomfort modulating visceral sensitivity or perception improving sensory perception of rectal distension or treating anal continence dysfunctions

22 A pharmaceutical composition for use in preventing modulating or treating visceral pain or discomfort modulating visceral sensitivity or perception improving sensory perception of rectal distension or treating anal continence dysfunctions which composition comprises a 5 HT_4 receptor agonist partial agonist or antagonist or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable diluents or carriers therefor

23 A method for preventing or treating gastro-intestinal motility disorders in horses or cattle in need thereof which method comprises administering to the horses or cattle an effective amount of a 5-HT_4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof

24 A 5-HT_4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof for use as a veterinary pharmaceutical or for use in the manufacture of a veterinary pharmaceutical

25 A pharmaceutical composition for veterinary use comprising a 5-HT_4 receptor agonist or partial agonist or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier therefor

26 A pharmaceutical composition comprising Tegaserod having dissolution characteristics in water or USP buffers pH 6 8 and 7 5 of

time (minutes)	amount (percentage)
5	30 90
15	80 100
30	95 100
60	100