

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

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

SOLICITUD
PUBLICADA

Número del expediente: 04-002774
Solicitante: ASTREZENECA AB
Apoderado: ALICIA LLOREDA RICAURTE
Título de la nueva creación o denominación del signo: Formulación farmacéutica que comprende un inhibidor de bomba de proton y antiácidos
Gaceta: 555

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

C.C. ☐ NT ☒
C.E. ☐ Otro ☐
Cual
Número 890.106.527-5

REPRESENTANTE
O APODERADO

Nombre: REINALDO PINILLA MORENO
Dirección: TRANVERSAL 13 A 119-95 OFICINA 104
Teléfono: 613 34 18 Fax: 24 47 87
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NT ☐
C.E. ☐ Otro ☐
Cual
Número 80425609 Tp 91563

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

5. Comprobante de pago No. _____

Fecha _____

6. ANEXOS

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

NOMBRE: REINALDO PINILLA MORENO

FIRMA: *Reinaldo Pinilla Moreno*

C.C. 80425609

TP. 91563 CSJ

PRESENTACION PERSONAL

En Bogotá, D.C. a 25 NOV 2005 se present.....

en la Notaría Décima, cuya encargada es MARIA JUDIT PRADO DIAZ

REINALDO PINILLA MORENO

Con cédula No. 80425609

Expedida en USA y dijo que

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

letra, En constancia se firmo *Reinaldo Pinilla Moreno*



Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 04-002774
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACION FARMACEUTICA QUE COMPRENDE
UN INHIBIDOR DE BOMBA DE PROTON Y
ANTIACIDOS".
Solicitante : ASTRAZENECA AB.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 555 del 31 de Agosto de 2005

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 **"FORMULACION FARMACEUTICA QUE COMPRENDE UN INHIBIDOR DE BOMBA DE PROTON Y ANTIACIDOS"**, solicitada por **ASTRAZENECA AB.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

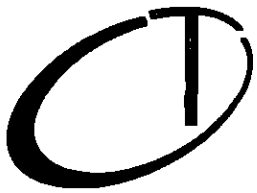
Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que pretende mi representada, en materia de omeprazol en particular. 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 16 de enero de 2004, reivindicando prioridad bajo las solicitudes EP01401896-4 del 2001-07-16 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 555 del 31 de agosto de 2005, página 404, N° publicación 417, cuya publicación internacional corresponde a la WO03/007917 del 2003-01-30.

2.2. La solicitud colombiana 04-002774 objeto de la presente oposición, se refiere a una tableta de multipartícula que se desintegra en la boca y que contiene:

- i) Un agente inhibidor de bomba de proton, en particular del tipo benzimidazole, en forma de microgránulos en capas de recubrimiento entérico que son recubiertos



ptimum

Derech de la C mpetencia, Propiedad Industrial y Comercio Exterior

47
108

con al menos un recubrimiento de barrera que proteja el recubrimiento entérico de la disolución y/o desintegración durante el transporte de los microgránulos al intestino delgado; ii) Al menos un antiácido en forma de gránulos, y; iii) Una mezcla de excipientes que comprenden al menos un agente desintegrador, un agente diluyente y un lubricante. El documento también se refiere a un proceso para la preparación de dicha tableta según cualquiera de las reivindicaciones 1 a 32, caracterizadas porque el inhibidor de bomba de proton se prepara en forma de microgránulos con recubrimiento entérico que son recubiertos por rociado con una capa barrera y mezclados con los gránulos del antiácido y una mezcla del agente desintegrador, el agente diluyente y un lubricante.

47
108
C. D. C. 108
C. D. C. 108

2.3. En primera instancia, se debe advertir que la reivindicación 36 y 37 se refieren al uso y al método terapéutico respectivamente y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...) "*, los usos no están contemplados como patentables; y, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*. Solo serán patentables los productos o procedimientos.

2.4. De otra 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: WO9725066, 1997-07-17.
- D2: US6106861, 2000-08-22
- D3: US6024981, 2000-02-15

2.5. Ahora bien, el documento D1, particularmente en el resumen y en la página 18, líneas 19 a 28 y el ejemplo 1, que se refiere a una dosis oral que comprende un ácido inhibidor de bomba de protones y uno o más agentes antiácidos. El inhibidor de bomba de protones está protegido por una capa de cubierta entérica y una sobre-cubierta y un antiácido formado en gránulos. Según D1, el material de la capa de sobre-cubierta es escogido de entre hidroxipropil celulosa, hidroxipropil metilcelulosa y polivinil acetato entre otros. La sobre-cubierta está diseñada según este documento D1, para prevenir la aglomeración y para proteger la capa de cubierta entérica. La formulación allí descrita puede ser en forma de múltiples unidades de dosificación. Así las cosas, es claro que este documento D1, revela una misma propuesta como solución que incluye un agente inhibidor de bomba de protones y al menos un antiácido en forma de gránulos. Por lo tanto, a los ojos de este documento D1, la presente solicitud no es novedoso.

2.6. Por su parte, el documento D2, particularmente en el resumen, columna 1, líneas 35 a 60 y columna 2 líneas 30 a 31 en conjunto con el ejemplo 1, revela una tableta multi-partícula de rápida desintegración en la boca en 40 segundos. El ingrediente activo está cubierto con un agente de cubierta. Según dicho documento D2, La tableta sólo contiene un agente soluble diluyente tal como manitol, sorbitol o maltitol y la cubierta del agente activo comprende al menos un polimetacrilato y un



ptimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

7
102

polímero celulosa. También se describe que el agente de desintegración es usado en conjunto con polivinilpirrolidona. De acuerdo con el ejemplo 1 de dicha solicitud D2, son usados saborizantes, endulzantes y lubricantes. Como se nota, cualquier persona versada en el arte puede deducir la conformación de una tableta multiparticula la cual comprende un inhibidor de bomba de protón y un antiácido usando la información que dicta este documento D2, donde el inhibidor de bomba de protón tiene una capa de separación, una cubierta entérica y una sobre-cubierta así como el antiácido presente en forma de gránulos, pues la tableta del documento D2, contiene un relleno, un desintegrador, sabor, endulzante y un lubricante y el resultado es una formulación que se desintegra en la boca al cabo de 40 segundos. Por lo tanto, este documento objeto de oposición a la luz del documento D2, carece de altura o nivel inventivo.

2.7.El documento D3 según el resumen y su descripción, revela el uso de cubiertas de ingredientes activos en tabletas las cuáles se disuelven rápidamente en la boca. Según este documento, se revela el uso del omeprazole en múltiples formas de dosificación. Por lo tanto, una persona versada en la materia, al relacionar lo referido en el documento D3 en conjunto con lo especificado en los documentos D1 y D2 puede llegar a lo pretendido en el presente documento objeto de oposición.

2.8.En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 04-002774 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

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

Calle 119 A N° 53-99. Tel. (571) 6 13 34 18 - 6 13 33 74 - Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

- 2.9.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 16 de julio de 2001, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, una tableta de rápida disolución que incluye un agente inhibidor de bomba de protón y al menos un antiácido en forma de gránulos sobre el cual busca protección en el capítulo reivindicatorio.
- 2.9.2. **CARENCIA DE ALTURA INVENTIVA** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 16 de julio de 2001, a partir de los documentos D1, D2, y D3 en combinación, es posible deducir la conformación de una tableta multipartícula la cual comprende un inhibidor de bomba de protón y un antiácido según lo definido en las reivindicaciones de la presente solicitud.
- 2.9.3. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el uso y el

método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

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

2.11. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada ***"FORMULACION FARMACEUTICA QUE COMPRENDE UN INHIBIDOR DE BOMBA DE PROTON Y ANTIACIDOS"***, solicitada por ***ASTRAZENECA AB***, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 555.

3. PRUEBAS

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

- D1: WO9725066, 1997-07-17.
- D2: US6106861, 2000-08-22
- D3: US6024981, 2000-02-15

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: WO9725066, 1997-07-17.
- D2: US6106861, 2000-08-22
- D3: US6024981, 2000-02-15

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 N° 119-95, Of. 104 de esta ciudad de Bogotá.

COLOMBIA
NOTARIO DECIMO
ENCARGADO
BOGOTA D. C.

Señor Superintendente,


REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

T.P.A. 91563 del C.S. de la J.

COLOMBIA
NOTARIO DECIMO
ENCARGADO
BOGOTA D. C.

PRESENTACION PERSONAL

En Bogotá, D.C. a 25 NOV 2005 se present.....

en la Notaría Décima, cuya encargada es MARIA JUDIT P/ RDO DIAZ

Reinaldo Pinilla Moreno

Con cédula No. 80425609

Expedida en LSA de y dijo que

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

letra, En constancia se firma 





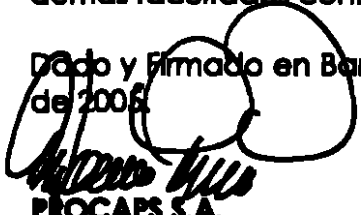
PODER ESPECIAL

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. 04-002774, de título: **"FORMULACION FARMACEUTICA QUE COMPRENDE UN INHIBIDOR DE BOMBA DE PROTON Y ANTIACIDOS"**, publicada en la gaceta No. 555 del 31 Agosto de 2005.

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.

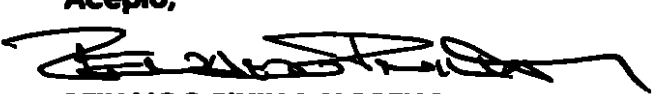
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 9 días del mes de noviembre de 2005.


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.

SEC. 101A NOTARIA SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANCILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Céntrica que este escrito fue
presentado Personalmente por Walter
Torales Tote Kawa

Identificado con: 16251923

Ejemplar en: Notaria

Quien declara que su contenido es cierto y que la
firma puesta es la suya

Firma

17 NOV. 2005

Huella del Comprobante

VERDADERO VERDADERO VERDADERO VERDADERO VERDADERO VERDADERO VERDADERO VERDADERO VERDADERO VERDADERO



Walter



***** Pag.01
CAMARA DE COMERCIO
DE BARRANQUILLA
06*****
CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 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 Publica Nro. 1307 del 28 de Junio de 1,979,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 baj
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 Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 bajo
el No. 12,705 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad de responsabilidad limitada bajo al raz n
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 baj
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 Publica Nro. 3615 del 6 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 baj

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

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

PROCAPS S.A. -----

el No. 67,218 del libro respectivo, la sociedad antes menci nada
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996,
ot rgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 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 documentos privados:

Numero	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004
416	3/ 3/2005	Notaria 2. de Barranquilla	116,364	3/10/2005
1,613	7/28/2005	Notaria 2. de Barranquilla	119,322	8/18/2005

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



***** Pag.02
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

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

PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion 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 los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos 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, de-

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

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

PROCAPS S.A. -----

desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL:	Nro. Acciones	Valor Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,220,000,000.00	1,220,000.00	1,000.00
PAGADO:		
\$*****1,220,000,000.00	1,220,000.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transaccion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con

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



***** Pag.03
CAMARA DE COMERCIO
DE BARRANQUILLA

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

PROCAPS S.A. -----

1 previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios 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 cuantía sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la transacción o celebración del acto. Las demás funciones que le correspondan como Representante Legal por disposición de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendrá 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 tendrá un Vicepresidente designado por la Junta Directiva, quien también ejercerá la representación legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendrá las siguientes 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 representación legal de la sociedad 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 interrogatorios 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 cuantía sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interés inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demás funciones que le correspondan como Representante legal por disposición de la ley, de estos estatutos de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con idénticas facultades y sin que sea necesario para

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

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

PROCAPS S.A. -----

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, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, 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. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados 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, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. -----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo,
y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales	Suplentes
1. Minski Gontovnik Ruben	Minski Zilberblum Elliot
2. Minski Gontovnik Meyer	Minski Deitel Daniel
3. Minski Gontovnik Jose	Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

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



***** Pag.04
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

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

PROCAPS S.A. -----

Cargo	Nombre	Identificacion
Presidente.	Minski Gontovnik Ruben	C.*****7,463,982=
Suplente del Presidente	Minski Minski Abraham	C.*****802,575=
Vicepresidente	Minski Gontovnik Meyer	C.*****7,461,324=
Suplente del vicepresidente	Minski Gontovnik Jose	C.*****8,671,834=

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificaci n
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

C E R T I F I C A

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

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

PROCAPS S.A. -----

Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Gerente.	Tanaka Walter	C.***16,251,923=

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, tor-
gada 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 respecti-
vo, 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 con-
fiere Poder Especial, Amplio y Suficiente a los senores: WALTER
TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA,
C.C. No. 8.715.941, para que cada uno en forma independiente en nom-
bre y representacion de PROCAPS S.A., suscriba todas las declaraci-
nes tributarias, aduaneras y cambiarias a que este obligada la so-
ciedad, asi como para que responda todo tipo de requerimiento o so-
licitudes de informacion de las autoridades tributarias, aduaneras o
cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se
confiere Poder Especial, amplio y suficiente, a los siguientes seno-
res que conforman el Grupo A y el Grupo B para que conjuntamente sus-
criban contratos de suministros de mercancias y servicios con enti-
dades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL
DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa re-
presentativa del mercado vigente en el dia que se realice la respec-
tiva 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 ME-
JIA 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 ejer-
cicio de estas facultades se requiera 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 Sufi-
ciente 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 Doc-
tor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno
representen a PROCAPS S.A., ante todo tipo de autoridades adminis-
trativas y judiciales, en asuntos de naturaleza cambiaria y fiscal,
tales como: Contestar e interponer demandas y requerimientos, com-

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



***** Pag.05
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

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

PROCAPS S.A. -----

parecer 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 celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones 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, inscrito 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, ampli 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 No.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 documentos 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

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

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

PROCAPS S.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, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado 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 señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representaci n 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 autoridades aduaneras en los ordenes distrital, departamental y naci - nal.-----

C E R T I F I C A

Que por Escritura Publica No.1.613 del 28 de Junio del 2.005, ot r - gada 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 conjuntamente suscriban contratos de suministro de mercancías 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 día 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 Camara de Comercio no aparecen inscripciones posteri res de documentos referentes a reforma, disolucion, liquidacion o nom - bramientos de representantes legales de la expresada sociedad.-----

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



***** Pag.06
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

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

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 23 de Marzo de 2,005. -----

La informacion sobre embargos de establecimientos se suministra en
Certificados de Matricula, la de contratos sujetos a registro, en
Certificados Especiales.

Maribel Reyes

NO CAUSA IMPUESTO DE TIMBRE

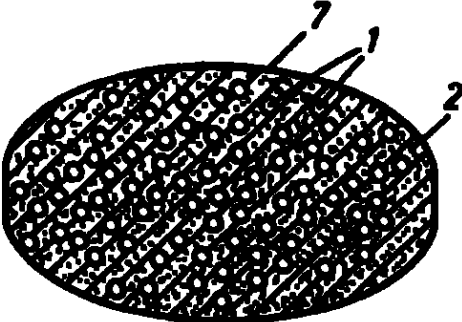
EL SECRETARIO
MARIBEL REYES OVIEDO

D1
114

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(31) International Patent Classification 6 : A61K 45/06, 31/44, 33/08, 33/10, 9/20, 9/26		A1	(11) International Publication Number: WO 97/25066 (43) International Publication Date: 17 July 1997 (17.07.97)
(21) International Application Number: PCT/SE96/01737 (22) International Filing Date: 20 December 1996 (20.12.96) (30) Priority Data: 9600071-6 8 January 1996 (08.01.96) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): DEPUJ, Helene [FR/SE]; Wrangelslagatan 7B, S-416 62 Göteborg (SE). HALLGREN, Agneta [SE/SE]; Hålsögårdsgatan 2C, S-431 38 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE).			(51) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GR, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.
(54) Title: ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE			
(57) Abstract An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor and one or more antacid agents or an alginate in a fixed formulation, wherein the proton pump inhibitor is protected by an enteric coating layer and an optional separating layer in between the proton pump inhibitor and the enteric coating. The fixed formulation is in the form of multilayered tablets, sachets or multiple unit tableted dosage forms. The multiple unit dosage form is most preferred. The new fixed formulation is especially useful in the treatment of disorders associated with dyspepsia such as heartburn.			
			

ORAL PHARMACEUTICAL DOSAGE FORMS COMPRISING A PROTON PUMP INHIBITOR AND AN ANTACID AGENT OR ALGINATE

Field of the invention

5 The present invention is related to new oral pharmaceutical preparations especially for use in the prevention and treatment of dyspeptic symptoms like upper abdominal pain/discomfort and heartburn. The present preparations comprise a combination of different gastric acid suppressing agents, such as an acid susceptible proton pump inhibitor and antacid agent(s) and /or an alginate in a new fixed unit dosage form, especially a
10 tableted dosage form. Furthermore, the present invention refers to a method for the manufacture of such preparations and the use of such preparations in medicine, especially in the treatment of dyspeptic symptoms.

Background of the invention

15

Dyspepsia is a common disorders and patients are seeing both gastroenterologists and general practitioners because of it. Heartburn is a symptom of dyspepsia, and it is estimated that 44% of Americans have heartburn at least monthly and some has to contact a doctor about the problem, but only around 25 % of the patients are seeing the doctor because of
20 their dyspepsia problem. Symptoms associated with dyspepsia symptom are for instance upper abdominal pain/discomfort and heartburn, indigestion, sour stomach, heartburn and other gastrointestinal disorders including gastro oesophageal reflux. The wide diversity of symptoms and disease severity produced by gastro oesophageal reflux has led to the need for more individualized treatment strategies.

25

Therapeutic agents effective in the treatment of dyspepsia include gastric acid suppressing agents, such as H₂ receptor antagonists, proton pump inhibitors, other agents of interest are antacids/alkalines and prokinetic agents. These agents can be distinguished by their mechanisms of action, safety profile, pharmacokinetics and indications.

WO 95/017080 describes a composition for use in the treatment of for instance heartburn, the composition comprises a H₂ receptor antagonist, such as famotidine, and an alginate and optionally simethicone.

5

Antacid agents and alginates may be used alone in the treatment of heartburn. They have a short duration of action but are seen as inexpensive and safe. Antacid agents work locally through a neutralisation of gastric acid. Alginates further give some mechanical protection against reflux of gastric acid into the oesophagus. The main advantages of antacid agents and alginates are, that they provide fast relief of symptoms. The main disadvantage of antacid agents and alginates is that, dosing has to be repeated frequently to keep the patients free of symptoms, further that antacids in many cases do not provide symptom resolution, i.e. complete relief of symptoms.

15 H₂ receptor antagonists are widely prescribed for reducing gastric acid secretion systemically. Proton pump inhibitors, such as omeprazole, are rapidly taking share from H₂ receptor antagonists. Omeprazole is known to offer significant gain over H₂ receptor antagonists in terms of symptom resolution, healing and prevention of relapse. Proton pump inhibitors provide symptom resolution, but normally not immediately.

20

Proton pump inhibitors have in clinical studies been proven to be very effective in providing symptom resolution (usually within 24 - 48 hours) in patients with dyspepsia associated with gastric ulcers, duodenal ulcers, reflux oesophagitis and gastro oesophageal reflux without oesophagitis. It is for instance established that omeprazole is superior to H₂ receptor antagonists regarding healing of gastroduodenal and oesophageal lesions as well as providing dyspeptic symptom resolution in these conditions, See Eriksson S., Euro Journ of Gastroenterology & Hepatology 1995, 7 : 465.

25 EP 338861 describes a solid pharmaceutical preparation of an antacid and excipients. It is proposed to use this preparation in combination with a proton pump inhibitor or any other

30

substance inhibit gastric acid secretion. There is no suggestion to combine these substances in one fixed unit dosage form.

US 5 244 670 describes an ingestible pharmaceutical composition comprising a substance
5 selected from the group consisting of antacid agents, acid secretion prevention agents, bismuth-containing agents, and mixtures thereof, and the excipient 3-1-menthoxy propane 1,2-diol. There are no specific arrangements discussed in neither of these references, to solve the problem with one of the component being an acid susceptible proton pump inhibitor.

10

A combination therapy of a proton pump inhibitor and an antacid or an alginate would provide immediate symptom relief, provided by the local effect of the antacid agent or the alginate, combined with a long-lasting symptom resolution provided by the systemically acting proton pump inhibitor. Such a combination would be ideal for "on-demand treatment
15 " of dyspepsia as well as for symptom resolution. The combination therapy comprising an acid suppressing agent, for instance a proton pump inhibitor, together with an antacid agent or an alginate could also be an alternative to each of them separately in case of failure.

It is well known that patient compliance is a main factor in receiving good results in medical
20 treatments. Administration of two or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The present invention now provides new oral dosage forms comprising two or more active substances combined in one fixed unit dosage form, preferably a tablet.

25 Some gastric acid suppressing agents, such as proton pump inhibitors, are susceptible to degradation/transformation in acid reacting and neutral media. In respect of the stability properties, it is obvious that the one of the active substances being a proton pump inhibitor must be protected from contact with acidic gastric juice by an enteric coating layer. There are different enteric coating layered preparations of proton pump inhibitors described in the

prior art, see for example US-A 4,786,505 (AB Hässle) describing a preparation comprising omeprazole.

There are problems to produce a fixed unit dosage form comprising a rather high amount of active substance. Different active substances in the same preparation give further problems. Preparation of a multiple unit tableted dosage form arises specific problems when enteric coating layered pellets comprising an acid susceptible proton pump inhibitor as active substance are compressed into tablets. If the enteric coating layer does not withstand the compression of the pellets into a tablet the susceptible active substance will be destroyed upon administration by penetrating acidic gastric juice, i.e. the acid resistance of the enteric coating layer of the pellets will not be sufficient in the tablet after compression.

Summary of the invention

The present invention provides oral, fixed unit dosage forms, i.e. multiple unit tableted dosage forms, layered formulations comprising an enteric coating layered tablet core, multilayered tablets or a sachet filled with more than one pharmaceutically active compound. The active compounds present in the dosage form are preferably an acid susceptible proton pump inhibitor and antacid agents. Alternatively, in some of the formulations the antacid agents may be replaced by an alginate. These new dosage forms will simplify the regimen and improve the patient compliance.

Brief description of the Figures

Fig. 1 illustrates a cross-section of a multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of enteric coating layered pellets (1) in admixture with antacid agent(s) and pharmaceutical excipients(2). Optionally, the tablet is covered by a filmcoating layer, i.e. tablet coat (7).

Fig. 2 illustrates a cross-section of a tablet with two separate layers, one of which comprising enteric coating layered pellets of an acid susceptible proton pump inhibitor (1) in admixture with excipients (3) and the other layer comprising a mixture of pharmaceutical excipients and an antacid agent(s) or an alginate (2). Optionally the layers are separated by an anti-tacking layer. Further the tablet is optionally covered by a filmcoating layer (7).

Fig. 3 illustrates a cross-section of a tablet comprising a mixture of pharmaceutical excipients and an acid susceptible proton pump inhibitor in the tablet core (5) surrounded by of an enteric coating layer (8) optionally with a separating layer applied in between the tablet core and the enteric coating layer and upon the enteric coating layer a layer of the antacid agent(s) in admixture with pharmaceutical excipients (6). Optionally, the tablet is covered by a filmcoating layer (7).

Detailed description of the invention

15

One object of the invention is to provide an oral, multiple unit tableted dosage form comprising an acid susceptible proton pump inhibitor in the form of individually enteric coating layered units together with one or more antacid agents in the form of a powder or granules compressed into a tablet. The enteric coating layer(s) covering the individual units of the acid susceptible proton pump inhibitor has properties such that the compression of the units into a tablet does not significantly affect the acid resistance of the individually enteric coating layered units. Furthermore, the multiple unit tableted dosage form provides a good stability to the active substances during long-term storage.

25 A further object of the invention is to provide a multiple unit tableted dosage form, which is divisible and easy to handle. Such a multiple unit tableted dosage form comprising enteric coating layered pellets of a proton pump inhibitor and antacid agent(s) also may be dispersed in a slightly acidic aqueous liquid and can be given to patients with swallowing disorders and in pediatrics. Such a suspension of dispersed units/pellets of appropriate size can be used for oral administration and also for feeding through a naso-gastric tube.

30

Another object of the invention is to provide a tablet preparation comprising a proton pump inhibitor in admixture with tablet excipients in a tablet core and a separate layer surrounding the tablet core, which layer comprises one or more antacid agent(s) in admixture with pharmaceutical excipients compressed onto the tablet core. The tablet core is enteric coating layered before the surrounding layer comprising the antacid agents is applied. Optionally a separating layer is applied on the tablet core before the core is enteric coating layered.

Alternatively, the prepared tablet is sectioned in separate layers, each one comprising different active substances. One of the layers comprises the proton pump inhibitor in the form of enteric coating layered pellets in admixture with pharmaceutical excipients and the other layer(s) comprises(-e) the antacid agent(s)/alginate, respectively in admixture with pharmaceutical excipients. Optionally the two layers are separated by a separating layer to prevent tacking between the two layers.

The new fixed unit dosage forms comprise as active substances one gastric acid suppressing agent, such as an acid susceptible proton pump inhibitor, and antacid agent(s)/alginate. Alternatively, the proton pump inhibitor in the form of enteric coating layered pellets may be mixed with an alginate and optionally pharmaceutical excipients to be administered in a sachet intended for oral administration after dispersion in a slightly acidic aqueous solution. The new fixed dosage form is preferably in the form of a multiple unit tableted dosage form containing enteric coating layered units comprising the active substance being an acid susceptible proton pump inhibitor and granules comprising the other active substance(s), i.e. the antacid agent(s) as shown in Fig. 1.

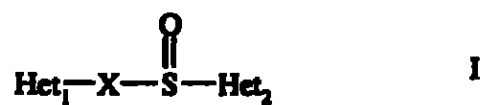
The antacid agent(s) may preferably be formulated in preparations intended for instant release. Alternatively, the components may be formulated in an effervescent formulation.

The different therapeutically active components used in the dosage forms are defined below.

Active substances

The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor.

Such proton pump inhibitors are for example compounds of the general formula I

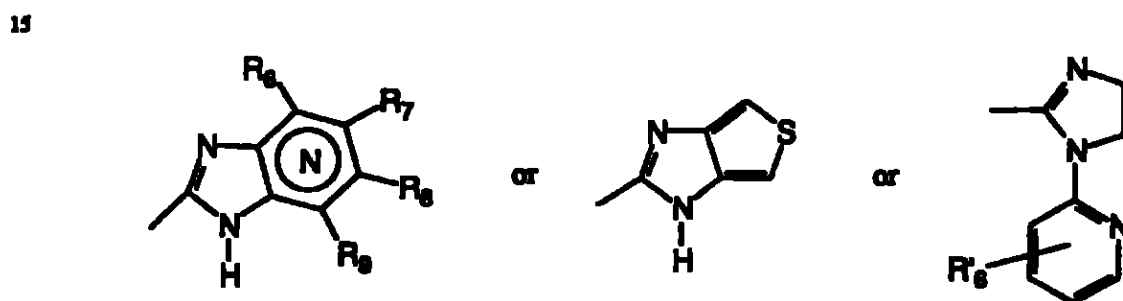


wherein

Het₁ is



Het₂ is



X =



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and aralkyl;

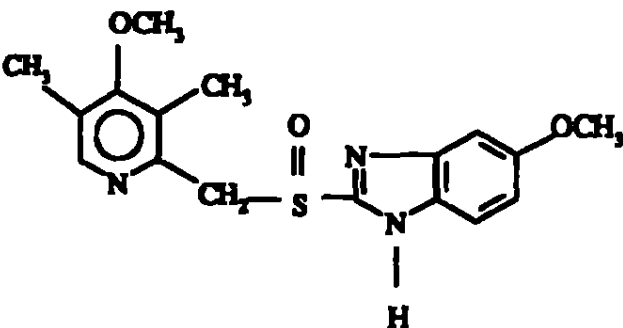
R₆' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;
R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C₁ - C₉ - chains or comprise cyclic alkyl groups, such as cycloalkylalkyl.

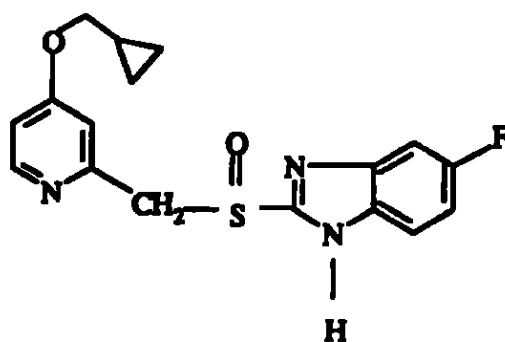
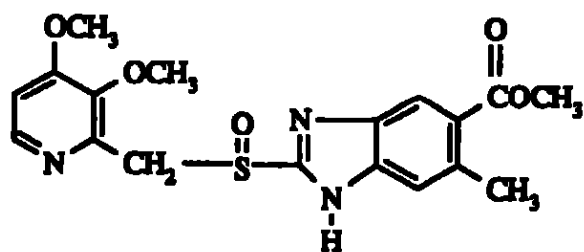
20

Examples of proton pump inhibitors according to formula I are

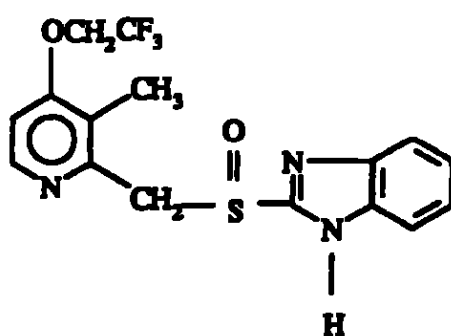


Omeprazole

9

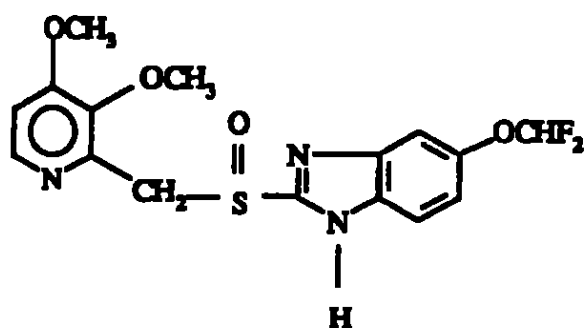


5

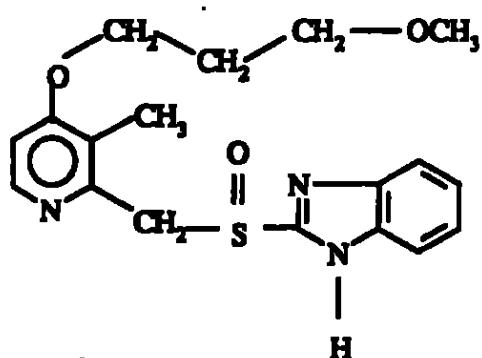


Lansoprazole

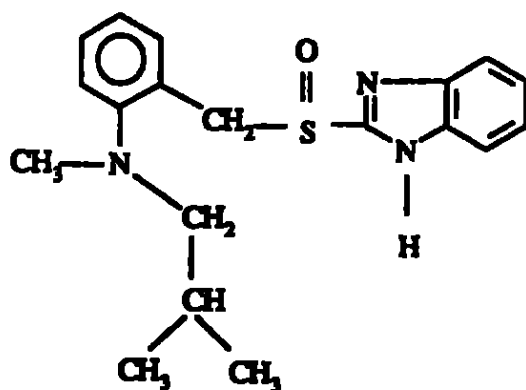
10



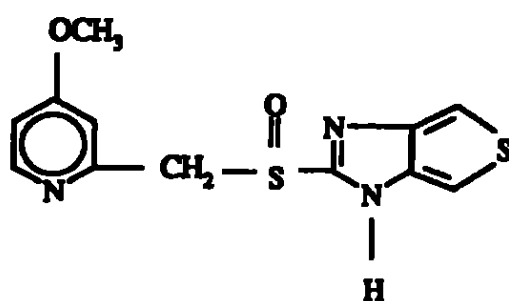
Pantoprazole

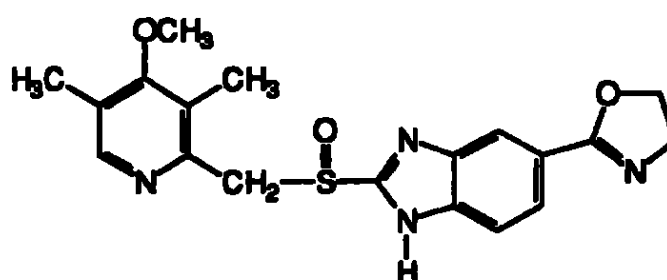
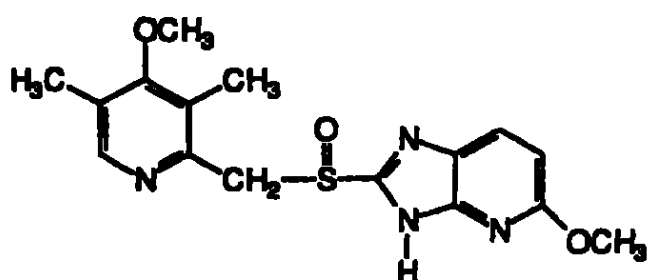
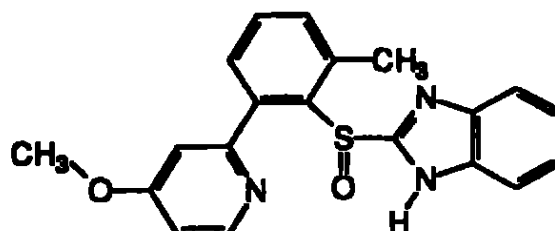
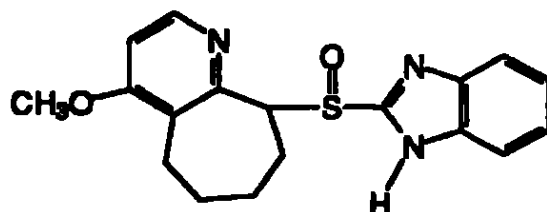


Pariprazole



Leminoprazole





- 10 The proton pump inhibitors used in the dosage forms of the invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ , K^+ or Li^+ salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, WO91/19711, WO91/19712, and further especially suitable compounds are described in WO95/01977 and
5 WO94/27988.

The gastric acid suppressing agent is preferably an acid susceptible proton pump inhibitor but H₂ receptor antagonists such as ranitidine, cimetidine or famotidine may be used in the pharmaceutical compositions with an alginate as proposed in WO 95/ 017080 or together
10 with antacid agent(s).

A wide variety of antacid agent(s) and/or alginates may be used in combination with a suitable proton pump inhibitor in the fixed unit dosage form according to the present invention. Such antacid agents include for example aluminium hydroxide, calcium
15 carbonate, magnesium hydroxide, magnesium carbonate and aluminium magnesium hydroxide carbonate (hydrotalcit) taken alone or in combinations with each other. The alginates may be an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salts, hydrates, esters etc. Especially preferred antacid agents are magnesium or calcium based antacid agents and aluminium hydroxide/magnesium
20 carbonate complex. Suitable antacid agents are for instance described in US 5 409 709.

The preferred multiple unit tableted dosage form comprising a proton pump inhibitor in the form of a racemat, an alkaline salt or one of its single enantiomers in combination with antacid agent(s), is characterized in the following way. Individually enteric coating layered
25 units (small beads, granules or pellets) containing the acid susceptible proton pump inhibitor and optionally containing alkaline reacting substances, are mixed with the antacid(s) and conventionally tablet excipients. The antacid(s) and tablet excipients may be dry mixed or wet-mixed into granules. The mixture of enteric coating layered units, antacid agent(s) and optionally excipients are compressed into the multiple unit tableted dosage forms. With the

expression "individual units" is meant small beads, granules or pellets, in the following referred to as pellets of the proton pump inhibitor.

The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coating layered pellets. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness of the enteric coating layer(s), must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished in that the acid resistance does not decrease more than 10% during the compression of the pellets into tablets.

10

The acid resistance is defined as the amount of proton pump inhibitor in the tablets or pellets after being exposed to simulated gastric fluid USP, or to 0,1 M HCl (aq) relative to that of unexposed tablets and pellets, respectively. The test is accomplished in the following way. Individual tablets or pellets are exposed to simulated gastric fluid of a temperature of 37°C. The tablets disintegrate rapidly and release the enteric coating layered pellets to the medium. After two hours the enteric coating layered pellets are removed and analyzed for content of the proton pump inhibitor using High Performance Liquid Chromatography (HPLC).

Further specific components used in the fixed unit dosage forms of the present invention are defined below.

Core material - for enteric coating layered pellets comprising a proton pump inhibitor

The core material for the individually enteric coating layered pellets can be constituted according to different principles. Seeds layered with the proton pump inhibitor, optionally mixed with alkaline substances, can be used as the core material for the further processing.

The seeds which are to be layered with the proton pump inhibitor can be water insoluble seeds comprising different oxides, celluloses, organic polymers and other materials, alone or

30

in mixtures or water-soluble seeds comprising different inorganic salts, sugars, non-pareils and other materials, alone or in mixtures. Further, the seeds may comprise the proton pump inhibitor in the form of crystals, agglomerates, compacts etc. The size of the seeds is not essential for the present invention but may vary between approximately 0.1 and 2 mm. The seeds layered with the proton pump inhibitor are produced either by powder or solution/suspension layering using for instance granulation or spray coating layering equipment.

Before the seeds are layered, the proton pump inhibitor may be mixed with further components. Such components can be binders, surfactants fillers, disintegrating agents, alkaline additives or other and/or pharmaceutically acceptable ingredients alone or in mixtures. The binders are for example polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl-cellulose (HPC), carboxymethylcellulose sodium, polyvinyl pyrrolidone (PVP), sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic or ionic surfactants such as for instance sodium lauryl sulfate.

Alternatively, the proton pump inhibitor optionally mixed with alkaline substances and further mixed with suitable constituents can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing conventional process equipment. The size of the formulated core material is approximately between 0.1 and 4 mm and preferably between 0.1 and 2 mm. The manufactured core material can further be layered with additional ingredients comprising the proton pump inhibitor and/or be used for further processing.

The proton pump inhibitor is mixed with pharmaceutical constituents to obtain preferred handling and processing properties and a suitable concentration of the substance in the final mixture. Pharmaceutical constituents such as fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives.

Further, the proton pump inhibitor may also be mixed with an alkaline, pharmaceutically acceptable substance (or substances). Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_4\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethyl-aminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material can be prepared by using spray drying or spray congealing technique.

15 Enteric coating layer(s)

Before applying the enteric coating layer(s) onto the core material in the form of individual pellets or tablets, the pellets or tablets may optionally be covered with one or more separating layer(s) comprising pharmaceutical excipients optionally including alkaline compounds such as pH-buffering compounds. This/these separating layer(s), separate(s) the core material from the outer layers being enteric coating layer(s). The separating layer(s) protecting the proton pump inhibitor should be water soluble or rapidly disintegrating in water.

25 The separating layer(s) can be applied to the core material by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating process. As an alternative the separating layer(s) can be applied to the core material by using powder coating technique. The materials for the separating layers are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl

25
130

acetate, hydroxypropyl cellulose, methylcellulose, ethyl-cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be
5 included into the separating layer(s).

When the optional separating layer, is applied to the core material it may constitute a variable thickness. The maximum thickness of the separating layer(s) is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and
10 may act as a pH-buffering zone. The pH-buffering properties of the separating layer(s) can be further strengthened by introducing into the layer(s) substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$,
15 $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$, aluminium hydroxide/sodium bicarbonate coprecipitate or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, carbonic, citric or other suitable, weak, inorganic or organic acids; or suitable organic bases, including basic amino acids and salts thereof. Talc or other
20 compounds may be added to increase the thickness of the layer(s) and thereby strengthen the diffusion barrier. The optionally applied separating layer(s) is not essential for the invention. However, the separating layer(s) may improve the chemical stability of the active substance and/or the physical properties of the novel multiple unit tableted dosage form.

25 Alternatively, the separating layer may be formed in situ by a reaction between an enteric coating polymer layer applied on the core material an alkaline reacting compound in the core material. Thus, the separating layer formed comprises a salt formed between the enteric coating layer polymer(s) and an alkaline reacting compound which is in the position to form a salt.

The separating layer may also be used to separate two different layers of a tablet, as described in Fig. 2

One or more enteric coating layers are applied onto the core material or onto the core material covered with separating layer(s) by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used, e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating polymer(s).

The enteric coating layers may contain pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers.

The amount of plasticizer is optimized for each enteric coating layer formula, in relation to selected enteric coating layer polymer(s), selected plasticizer(s) and the applied amount of said polymer(s), in such a way that the mechanical properties, i.e. flexibility and hardness of the enteric coating layer(s), for instance exemplified as Vickers hardness, are adjusted so that the acid resistance of the pellets covered with enteric coating layer(s) does not decrease significantly during compression of pellets into tablets. The amount of plasticizer is usually above 10 % by weight of the enteric coating layer polymer(s), preferably 15 - 50 % and more preferably 20 - 50 %. Additives such as dispersants, colorants, pigments polymers e.g. poly (ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material.

To protect the acid susceptible substance, the proton pump inhibitor, and to obtain an acceptable acid resistance of the dosage form according to the invention, the enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating is normally limited by processing conditions and the desired dissolution profile.

Alternatively, the enteric coating layer described above may also be used for enteric coating of conventional tablets comprising an acid susceptible proton pump inhibitor. Said enteric coating layered tablet is thereafter presscoated with antacid granules and pharmaceutical excipients.

Over-coating layer

Pellets covered with enteric coating layer(s) may further be covered with one or more over-coating layer(s). The over-coating layer(s) should be water soluble or rapidly disintegrating in water. The over-coating layer(s) can be applied to the enteric coating layered pellets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for over-coating layers are chosen among pharmaceutically acceptable compounds such as, for instance sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such for instance magnesium stearate, titaniumdioxide, talc and other additives may also be included into the over-coating layer(s). Said over-coating layer may further prevent potential agglomeration of enteric coating layered pellets, further protect the enteric coating layer towards cracking during the compaction process and enhance the tableting process. The maximum thickness of the applied over-coating layer(s) is normally limited by processing conditions and the desired dissolution profile.

The above described over-coating layer may also be used as a tablet filmcoating layer to obtain tablets of good appearance.

5 Antacid agent(s) or alginate preparation

The active substance in form of one or more antacid agent(s) are dry mixed with inactive excipients such as fillers, binders, disintegrants, and other pharmaceutically acceptable additives. The mixture is wet massed with a granulation liquid. The wet mass is dried
10 preferably to a loss on drying of less than 3% by weight. Thereafter the dry mass is milled to a suitable size for the granules, such as smaller than 4 mm, and preferably smaller than 1 mm. Suitable inactive excipients are for instance mannitol, corn starch, potato starch, low substituted hydroxypropylcellulose, microcrystalline cellulose and crosslinked polyvinylpyrrolidone. The dry mixture comprising antacid agent(s) is mixed with a suitable
15 granulation liquid comprising for instance hydroxypropylcellulose or polyvinylpyrrolidone dissolved in purified water or alcohol or a mixture thereof.

Alternatively, the antacid agent(s) are dry mixed with pharmaceutically acceptable excipients according to the above. The alginate preparation should also be prepared by dry
20 mixing with pharmaceutically acceptable excipients.

Multiple unit tablets

The enteric coating layered pellets comprising a proton pump inhibitor are mixed with the
25 prepared antacid granules or with the prepared dry mixture comprising the antacid agent(s). The mixture is admixed with lubricant(s) and compressed into a multiple unit tableted dosage form. Suitable lubricants for the tableting process are for instance sodium stearyl fumarate, magnesium stearate and talc. The compressed tablet is optionally covered with a filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the
30 stability of the tablet during packaging and transport. Such a coating layer may further

comprise additives such as anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

Further, the different active substances may be formulated into different layers, wherein the
5 layer comprising the proton pump inhibitor preferably is in the form of a multiple unit
tableted dosage form layered with the prepared mixture of the antacid agent(s) or an
alginate preparation. The two layers may be separated by a third layer comprising anti-
tacking agents.

10 The fraction of enteric coating layered pellets constitutes less than 75 % by weight of the
total tablet weight and preferably less than 60 %. By increasing the amount of the granules
comprising the antacid agent(s) and excipients, the fraction of enteric coating layered pellets
of the proton pump inhibitor may be reduced in the multiple unit tableted dosage form. By
choosing small enteric coating layered pellets in the formulation according to the present
15 invention, the number of pellets in each tablet can be held high which in turn makes the
tablet divisible with retained dosing accuracy.

Thus, the preferred multiple unit tablet formulation consists of enteric coating layered
pellets containing the acid susceptible proton pump inhibitor, optionally in admixture with
20 alkaline reacting compound(s), compressed into tablets together with the prepared antacid
mixture and optionally tablet excipients. The addition of an alkaline reacting material to the
proton pump inhibitor is not necessary, in any sense, but such a substance may further
enhance the stability of the proton pump inhibitor or some of the alkaline reacting
compounds may react in situ with the enteric coating material to form a separating layer.

25 The enteric coating layer(s) is making the pellets of the dosage form insoluble in acidic
media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance
the liquids present in the proximal part of the small intestine, where dissolution of the
proton pump inhibitor is desired. The enteric coating layered pellets may further be covered
with an overcoating layer before being formulated into the tablet and they may also contain

one or more separating layer(s) in between the core material and the enteric coating layer(s).

Process

5

The process for the manufacture of the dosage form represents a further aspect of the invention. After formulation of the pellets by spray coating or layering of the proton pump inhibitor onto seeds, or by extrusion/spheronization or granulation, e.g. rotor granulation of homogeneous pellets, the pellets are first optionally covered with the separating layer(s) and then with the enteric coating layer(s) or a separating layer is spontaneously developed in situ between the core material and the enteric coating layer material. The coating is carried out as described above and in the accompanying examples. The preparation of the antacid mixture is also described above and in the examples. The pharmaceutical processes can preferably be completely water-based.

15

The enteric coating layered pellets, with or without an over-coat, are mixed with the prepared antacid granules, tablet excipients and other pharmaceutically acceptable additives and compressed into tablets. Alternatively, the enteric coating layered pellets may be intimately mixed with tablet excipients and precompressed and further layered with the antacid or alginate preparation and finally compressed into a tablet. As a further alternative the proton pump inhibitor in form of a powder may be mixed with tablet excipients and compressed into a tablet which is optionally layered with a separating layer and thereafter enteric coating layered. Said tablet core is then presscoated with the antacid preparation. Finally the tablet may be covered by a tablet coat.

25

As a further alternative, the proton pump inhibitor in the form of enteric coating layered pellets may be filled in a sachet together with an alginate optionally mixed with excipients.

-4+
136

Use of the preparation

The dosage forms according to the invention are especially advantageous in the treatment of dyspepsia and other gastrointestinal disorder to provide an immediate symptom relief and a long-lasting symptom resolution. The dosage forms are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active substances varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.1-200 mg of the proton pump inhibitor and 0.1-1000 mg of the antacid agent(s)/alginate. Preferably, each dosage form will comprise 5-80 mg of the proton pump inhibitor and 100-900 mg of the antacid agent(s)/alginate, and more preferably 10-40 mg of proton pump inhibitor and 250 - 650 mg of the antacid agent(s)/alginate, respectively.

The multiple unit tablet preparation is also suitable for dispersion in an aqueous liquid with slightly acidic pH-value before being orally administered or fed through a naso-gastric tube.

The invention is illustrated more in detail in the following examples.

Examples

Example 1:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents (batch size 400 tablets).

Core material

Magnesium omeprazole	5.0	kg
Sugar sphere seeds	10.0	kg
Hydroxypropyl methylcellulose	0.75	kg
Water purified	20.7	kg

42
137

Separating layer

	Core material (acc. to above)	10.2	kg
	Hydroxypropyl cellulose	1.02	kg
	Talc	1.75	kg
5	Magnesium stearate	0.146	kg
	Water purified	21.4	kg

Enteric coating layer

	Pellets covered with separating layer (acc. to above)	11.9	kg
10	Methacrylic acid copolymer (30 % suspension)	19.8	kg
	Triethyl citrate	1.79	kg
	Mono- and diglycerides (NF)	0.297	kg
	Polysorbate 80	0.03	kg
	Water purified	11.64	kg

15

Over-coating layer

	Enteric coating layered pellets (acc. to above)	20.0	kg
	Hydroxypropyl methylcellulose	0.238	kg
	Magnesium stearate	0.007	kg
20	Water purified	6.56	kg

Tablets

	Prepared pellets comprising omeprazole Mg-salt (acc. to above)	31.3	g
	Microcrystalline cellulose	140.0	g
25	Calcium carbonate	100.0	g
	Aluminium hydroxide/magnesium carbonate	100.0	g
	Potato starch	46.4	g
	Water purified	314	g
	Polyvidone crosslinked	38.0	g
30	Sodium stearyl fumarate	4.6	g

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

5

The prepared core material was covered with a separating layer of a hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed
10 apparatus. In a fluid bed apparatus enteric coating layered pellets were coated with a hydroxypropyl methylcellulose containing magnesium stearate. The over-coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in purified hot water to form the
15 granulation liquid. Calcium carbonate, aluminium hydroxide/magnesium carbonate, potato starch and microcrystalline cellulose are dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 50°C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

20 The enteric coating layered pellets with an over-coating layer, prepared granules, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 10 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 110N.

25

Optionally the obtained tablets were covered with a tablet coating layer.

Results

"Acid resistance" i.e. % left after exposure to 0.1 N HCl for 2 hrs	
	Tablets
Ex 1	93%

5 Example 2:

Multiple unit tableted dosage form comprising magnesium omeprazole and antacid agents
(batch size 500 tablets).

10 Core material

Magnesium omeprazole	10.0 kg
Sugar sphere seeds	10.0 kg
Hydroxypropyl methylcellulose	1.5 kg
Water purified	29.9 kg

15**Separating layer**

Core material (acc. to above)	20.0 kg
Hydroxypropyl cellulose	2.0 kg
Talc	3.43 kg

20 Magnesium stearate

Water purified	41.0 kg
----------------	---------

Enteric coating layer

Pellets covered with separating layer (acc. to above)	24.5 kg
---	---------

	Methacrylic acid copolymer (30 % suspension)	32.7 kg
	Triethyl citrate	2.94 kg
	Mono- and diglycerides (NF)	0.49 kg
	Polysorbate 80	0.049 kg
5	Water purified	19.19 kg

Over-coating layer

	Enteric coating layered pellets (acc. to above)	37.8 kg
	Hydroxypropyl methylcellulose	0.49 kg
10	Magnesium stearate	0.0245 kg
	Water purified	11.6 kg

Tablets

	Prepared pellets comprising magnesium omeprazole (acc. to above)	47.45 g
15	Calcium carbonate	123.9 g
	Magnesium hydroxide	123.9 g
	Potato starch	52.2 g
	Water purified	435 g
	Microcrystalline cellulose	175 g
20	Polyvidone crosslinked	50 g
	Sodium stearyl fumarate	6.0 g

Enteric coating layered pellets of magnesium omeprazole with an overcoating layer were prepared as in Example 1.

25

A small amount of the potato starch was dissolved in hot purified water to form the granulation liquid. Calcium carbonate, magnesium hydroxide and potato starch were dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed. The wet mass was dried in a steamoven at 40 °C. The prepared granulation was milled
30 through sieve 1 mm in an oscillating mill equipment.

The enteric coated layered pellets with an over-coating layer, prepared granules, microcrystalline cellulose, polyvidone crosslinked and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of omeprazole in each tablet was approx. 20 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 30-40N.

Optionally the obtained tablets were covered with a tablet coating layer.

10 Example 3:

Multiple unit tableted dosage form comprising S-omeprazole magnesium salt and antacid agents (batch size 500 tablets).

15 Core material

S-omeprazole magnesium salt	120 g
Sugar sphere seeds	150 g
Hydroxypropyl methylcellulose	18 g
Polysorbate 80	2.4 g
20 Water purified	562 g

Separating layer

Core material (acc. to above)	200 g
Hydroxypropyl cellulose	30 g
25 Talc	51.4 g
Magnesium stearate	4.3 g
Water purified	600 g

Enteric coating layer

30 Pellets covered with separating layer (acc.to above)	250 g
--	-------

	Methacrylic acid copolymer (30% suspension)	333.7 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
5	Water purified	196 g

Tablets

	Prepared pellets comprising (s)-omeprazole Mg-salt	63.7 g
	Calcium carbonate	123.9 g
10	Magnesium hydroxide	123.9 g
	Potato starch	52.2 g
	Water purified	435 g
	Microcrystalline cellulose	175 g
	Polyvidone crosslinked	50.0 g
15	Sodium stearyl fumarate	6.0 g

Suspension layering was performed in a fluid bed apparatus. S-omeprazole magnesium salt was sprayed onto sugar sphere seeds from a water suspension containing the dissolved binder and polysorbate 80. The size of sugar sphere seeds were in the range of 0.25 to 0.35 mm.

The prepared core material was covered with a separating layer in a fluid bed apparatus with hydroxypropyl cellulose solution containing talc and magnesium stearate. The enteric coating layer consisting of methacrylic acid copolymer, mono-and diglycerides, triethyl citrate and polysorbate was sprayed onto the pellets covered with a separating layer in a fluid bed apparatus. The enteric coating layered pellets were classified by sieving.

A small amount of the potato starch was dissolved in hot purified water to form the granulation liquid. Calcium carbonate, magnesium hydroxide and potato starch were dry-mixed. The granulation liquid was added to the dry mixture and the mass was wet-mixed.

The wet mass was dried in a steamoven at 40 °C. The prepared granulation was milled through sieve 1 mm in an oscillating mill equipment.

The enteric coating layered pellets, prepared granules, polyvidone crosslinked, microcrystalline cellulose and sodium stearyl fumarate were mixed and compressed into tablets using a tableting machine equipped with 9x20 mm oval punches. The amount of S-omeprazole in each tablet was approx. 20 mg and the amount of antacid agents were approx. 500 mg in total. Tablet hardness was measured to 30N.

Optionally the obtained tablets were covered with a tablet coating layer.

Example 4:

Three-layered tableted dosage form with a fast disintegrating layer comprising omeprazole, a separating layer and a layer comprising alginic acid. (batch size 1 000 tablets)

Tablets

First tablet layer

Alginic acid	500 g
Sodium hydrogencarbonate	150 g
Microcrystalline cellulose	87 g
Polyvinyl pyrrolidone crosslinked	13 g
Sodium stearyl fumarate	3.8 g

Separating layer

Microcrystalline cellulose	80 g
----------------------------	------

Second tablet layer

Enteric coating layered pellets comprising omeprazole Mg-salt	78.3 g
---	--------

(manufacturing and composition as in example 1)

Microcrystalline cellulose	174 g
Polyvinyl pyrrolidone crosslinked	26 g
Sodium stearyl fumarate	1.4 g

5

Alginic acid, sodium hydrogencarbonate, microcrystalline cellulose, polyvinyl pyrrolidone and sodium stearyl fumarate were dry-mixed and precompressed as a first layer in a tableting machine equipped with 10x21 mm oval punches. Microcrystalline cellulose was filled on top of the first layer to form a separating layer to the next layer.

10

The enteric coating layered pellets, microcrystalline cellulose, polyvinyl pyrrolidone and sodium stearyl fumarate were dry-mixed and filled on top of the separating layer. The three layers were compressed into a three layers tablet.

15

Optionally the tablet was covered by a tablet coating layer.

The amount of omeprazole in each tablet is approx. 10 mg and the amount of alginic acid was approx 500 mg.

20

The best mode to practise the invention is described in Examples 1 and 4.

The enteric coating layered pellets comprising a proton pump inhibitor may also be prepared as described in the following examples.

25

Example 5

Preparation of enteric coating layered pellets by extrusion/spheronization.

Core material

	Magnesium omeprazole	600 g
	Mannitol	1000 g
	Microcrystalline cellulose	300 g
5	Hydroxypropyl cellulose	100 g
	Sodium lauryl sulphate	6 g
	Water purified	802 g

Separating layer

10	Core material	400 g
	Hydroxypropyl methylcellulose	48 g
	Water purified	960 g

Enteric coating layer

15	Pellets covered with separating layer	200 g
	Methacrylic acid copolymer	100 g
	Triethyl citrate	30 g
	Mono- and diglycerides (NF)	5 g
	Polysorbate 80	0.5 g
20	Water purified	309 g

Sodium lauryl sulphate is dissolved in purified water to form the granulation liquid.

Magnesium omeprazole, mannitol, microcrystalline cellulose and hydroxypropyl cellulose are dry-mixed. The granulation liquid is added to the powder mixture and the mass is wet-
25 mixed. The wet mass is forced through an extruder equipped with screens of size 0.5 mm. The extrudate is spheronized on a friction plate in a spheronizing apparatus. The core material is dried in a fluid bed dryer and classified. The prepared core material is covered by a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose/water solution.

51
146

The enteric coating layer is applied to the pellets covered with separating layer from an aqueous dispersion of methacrylic acid copolymer plasticized with triethyl citrate to which a mono- and diglycerides/polysorbate dispersion has been added. The pellets are dried in a fluid bed apparatus.

5

Example 6

Preparation of enteric coating layered pellets by powder layering of sugar sphere seeds.

10	<u>Core material</u>	
	Magnesium omeprazole	1 500 g
	Sugar sphere seeds	1 500 g
	Hydroxypropyl methylcellulose	420 g
	Aerosil®	8 g
15	Water purified	4 230 g
	<u>Separating layer</u>	
	Core material	500 g
	Hydroxypropyl cellulose	40 g
20	Talc 67 g	
	Magnesium stearate	6 g
	Water purified	800 g
	<u>Enteric coating layer</u>	
25	Pellets covered with separating layer	500 g
	Methacrylic acid copolymer	200 g
	Triethyl citrate	60 g
	Water purified	392 g

Magnesium omeprazole, part of the hydroxypropyl methylcellulose and Aerosil® are dry-mixed forming a powder. Sugar sphere seeds (0.25-0.40 mm) are layered with the powder in a centrifugal fluidized coating granulator while spraying a hydroxypropyl methylcellulose solution (6 %, w/w).

5

The prepared core material is dried and covered by a separating layer in a centrifugal fluidized coating-granulator. A fluid bed apparatus is used for enteric coating layering.

Example 7

10

Preparation of enteric coating layered pellets with cores of silicon dioxide seeds.

Core material

	Magnesium omeprazole	8.00 kg
15	Silicon dioxide	8.00 kg
	Hydroxypropyl methylcellulose	1.41 kg
	Sodium lauryl sulphate	0.08 kg
	Water purified	28.00 kg

20 Separating layer

	Core material (acc. to above)	10.00 kg
	Hydroxypropyl methylcellulose	0.80 kg
	Water purified	10.00 kg

25 Enteric coating layer

	Pellets covered with separating layer (acc. to above)	300 g
	Methacrylic acid copolymer	124 g
	Polyethylene glycol 400	25 g
	Mono- and diglycerides (NF)	3 g
30	Polysorbate 80	1 g

Water purified 463 g

Suspension layering is performed in a fluid bed apparatus. Magnesium omeprazole is sprayed onto the silicon dioxide seeds from a water suspension containing the dissolved
5 binder and a surface active ingredient.

The prepared core material is covered with a separating layer in a fluid bed apparatus with a hydroxypropyl methylcellulose solution. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, polyethylene glycol 400 and polysorbate is sprayed
10 onto the pellets covered with separating layer in a fluid bed apparatus.

Example 8

Preparation of enteric coating layered pellets.

15

Enteric coating layer

Pellets covered with separating layer
(manufacturing and composition
as in example 10)

20

	500 g
Methacrylic acid copolymer	250 g
Polyethylene glycol 6000	75 g
Mono- and diglycerides (NF)	12.5 g
Polysorbate 80	1.2 g
Water purified	490 g

25

Example 9

Preparation of enteric coating layered pellets.

Enteric coating

Pellets covered with separating layer 500 g

(manufacturing and composition as in example 1)

Hydroxypropyl methylcellulose phthalate 250 g

5 Cetanol 50 g

Ethanol (95%) 1000 g

Acetone 2500 g

Example 10

10

Preparation of enteric coating layered pellets.

Core material

Omeprazole 225 g

15 Mannitol 1425 g

Hydroxypropyl cellulose 60 g

Microcrystalline cellulose 40 g

Lactose anhydrous 80 g

Sodium lauryl sulphate 5 g

20 Disodium hydrogen phosphate dihydrate 8 g

Water purified 350 g

Separating layer

Core material 300 g

25 Hydroxypropyl cellulose 30 g

Talc 51 g

Magnesium stearate 4 g

Enteric coating layer

30 Pellets covered with separating layer 300 g

58

Methacrylic acid copolymer	140	g
Triethyl citrate	42	g
Mono- and diglycerides (NF)	7	g
Polysorbate 80	0.7	g

5

The dry ingredients for producing the core material are well mixed in a mixer. Addition of granulation liquid is made and the mixture is kneaded and granulated to a proper consistency. The wet mass is pressed through an extruder screen and the granules are converted into a spherical form in a spheronizer. The core material is dried in a fluid bed apparatus and classified into a suitable particle size range, e.g. 0.5 - 1.0 mm. The prepared core material is covered with a separating layer and enteric coating layered as described in previous examples.

10

Preparation of active substance.

15

Magnesium omeprazole used in some of the examples is produced according to the process described in WO95/01977, the single enantiomers of omeprazole salts are prepared as described in WO94/27988 and omeprazole is produced according to the process disclosed in EP-A1 0005129. These documents are hereby incorporated in a whole by reference.

CLAIMS

1. An oral pharmaceutical dosage form comprising an acid susceptible proton pump inhibitor together with one or more antacid agents or alginates and optionally
3 pharmaceutically acceptable excipients, characterized in that the dosage form is in the form of a fixed unit dosage form comprising at least two pharmaceutically active components and wherein the proton pump inhibitor is protected by an enteric coating layer.
2. A dosage form according to claim 1, wherein the dosage form is a tablet
10 formulation.
3. A dosage form according to claim 1, wherein the dosage form is a sachet formulation.
- 15 4. A dosage form according to claim 1, wherein the proton pump inhibitor is protected by two layers, an enteric coating layer and a layer separating the enteric coating from the proton pump inhibitor.
5. A dosage form according to claim 1, wherein the dosage form comprises an acid
20 susceptible proton pump inhibitor and two antacid agents.
6. A dosage form according to claim 1, wherein the proton pump inhibitor is omeprazole, one of its single enantiomers or an alkaline salt thereof.
- 25 7. A dosage form according to claim 6, wherein the proton pump inhibitor is (s)-omeprazole magnesium salt.
8. A dosage form according to claim 1, wherein the proton pump inhibitor is lansoprazole, one of its single enantiomers or an alkaline salt thereof.

- 59
152
9. A dosage form according to one of claims 6 - 8, wherein the antacid agents are aluminium hydroxide in combination with magnesium carbonate.
10. A dosage form according to any of claims 6 - 8, wherein the antacid agents are
5 magnesium hydroxide in combination with calcium carbonate.
11. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 5-80 mg and the amount of antacid/alginate is in the range of 100-900 mg.
- 10 12. A dosage form according to claim 1, wherein the amount of proton pump inhibitor is in the range of 10-40 mg and the amount of antacid/alginate is in the range of 250-650 mg.
13. A tableted dosage form according to claim 2, wherein the dosage form consists of two separate layers optionally separated by a separating layer, and one layer comprising a
15 proton pump inhibitor and the other layer comprising one or more antacid agents or alginates.
14. A tableted dosage form according to claim 2, wherein the tablet formulation is a multiple unit tableted dosage form comprising the acid susceptible proton pump inhibitor in
20 the form of enteric coating layered pellets compressed together with a antacid preparation into a tablet, whereby the enteric coating layer covering the individual pellets has mechanical properties such that the tableting of the pellets together with the antacid preparation and optionally pharmaceutically acceptable excipients does not significantly affect the acid resistance of the enteric coating layered pellets.
- 25 15. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets is in coherence with the requirements on enteric coating layered articles defined in the United States Pharmacopeia.

16. A tableted dosage form according to claim 14, wherein the acid resistance of the enteric coating layered pellets does not decrease more than 10 % during the compression of the pellets into the multiple unit tableted dosage form.

5 17. A tableted dosage form according to claim 14, wherein the enteric coating of the pellets comprises a plasticized enteric coating layer material.

18. A tableted dosage form according to claim 14, wherein the enteric coating layered pellets are further covered with an over-coating layer comprising pharmaceutically
10 acceptable excipients.

19. A tableted dosage form according to claim 14, wherein the tablet is divisible.

20. A tableted dosage form according to claim 19, wherein the tablet is dispersible to an
15 aqueous suspension comprising antacid agent(s) and enteric coating layered pellets of a proton pump inhibitor.

21. A tableted dosage form according to claim 2, wherein the tablet is an enteric coating layered tablet comprising the proton pump inhibitor surrounded by a layer comprising the
20 antacid preparation.

22. A tableted dosage form according to claim 14, wherein the proton pump inhibitor is in the form of a multiple unit tableted dosage form surrounded with a separate layer comprising the antacid agent(s) or an alginate preparation.

25

23. A process for the manufacture of a fixed dosage form comprising an acid susceptible proton pump inhibitor in one layer and one or more antacid agents or an alginate in another layer, characterized in that the proton pump inhibitor is prepared in the form of enteric coating layered pellets, the pellets are mixed with pharmaceutically acceptable excipients

and precompressed and further layered with a surrounding layer of an antacid or an alginate preparation and finally compressed into a tablet.

24. A process for the manufacture of a fixed dosage form comprising an acid susceptible
5 proton pump inhibitor and one or more antacid agents in a multiple unit tableted dosage
form, characterized in that the proton pump inhibitor is prepared in the form of enteric
coating layered pellets and these pellets are mixed with an antacid preparation and
optionally pharmaceutically acceptable tablets excipients whereafter the dry mixture is
compressed into a multiple unit tablet without giving any significant change of the acid
10 resistance of the enteric coating layer.

25. A process for the manufacture of a fixed dosage form comprising an acid susceptible
proton pump inhibitor and one or more antacid agent(s) in an enteric coating layered tablet
characterized in that the proton pump inhibitor is admixed with tablet excipients and
15 compressed into a tablet, which tablet is covered with an enteric coating layer and
optionally a separating layer has applied onto the tablet before the enteric coating layer, the
antacid agent(s) mixed with pharmaceutically acceptable excipients are thereafter
compressed onto the enteric coating layered tablet.

26. A method for the treatment of disorders associated with dyspepsia in mammals and
20 man by administering to a host in need thereof a therapeutically effective dose of a multiple
unit tableted dosage form according to any of claims 1 to 22.

27. A method according to claim 26, wherein the disorder is a gastric disorder
25 associated with heartburn.

28. Use of a dosage form according to any of claims 1 to 22 for the manufacture of a
medicament for the treatment of disorders associated with dyspepsia.

29. Use according to claim 28, wherein the disorder is a gastric disorder associated with heartburn.

Fig. 1

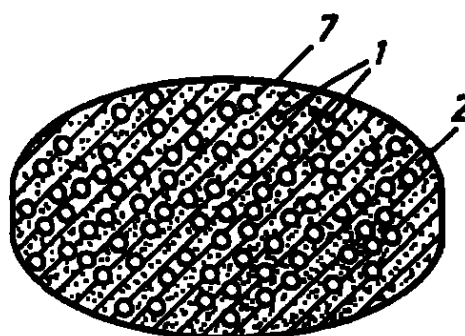


Fig. 2

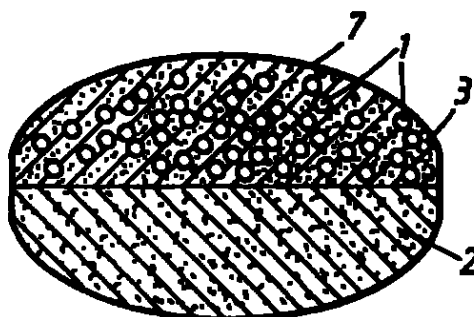
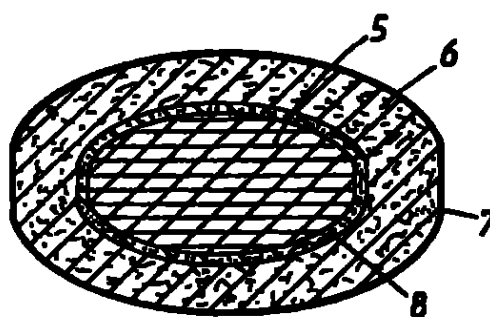


Fig. 3





US006106861A

United States Patent [19]
Chauveau et al.

[11] Patent Number: 6,106,861
[45] Date of Patent: *Aug. 22, 2000

- [54] **MULTIPARTICULATE TABLET
DISINTEGRATING IN LESS THAN 40
SECONDS IN THE MOUTH**
- [75] **Inventors:** Charles Chauveau, Valbonne;
Edouard Gendrot, Garnay; Alain
Gilles Demichella, Grasse; Nouredidine
Nouri, Vallauris, all of France
- [73] **Assignee:** Laboratoires Prographarm,
Chateaufort en Thymerais, France
- [*] **Notice:** This patent issued on a continued pro-
secution application filed under 37 CFR
1.53(d), and is subject to the twenty year
patent term provisions of 35 U.S.C.
154(a)(2).

[21] Appl. No.: 08/985,793

[22] Filed: Dec. 5, 1997

[30] Foreign Application Priority Data

Jul. 21, 1997 [FR] France 97 09233

[51] Int. Cl.⁷ A61K 9/20; A61K 9/14;
A61K 9/16

[52] U.S. Cl. 424/465; 424/494; 424/497;
514/960

[58] Field of Search 424/464, 465,
424/470, 474, 479, 489, 493, 494, 497,
469; 514/960

[56] References Cited

U.S. PATENT DOCUMENTS

2,887,437 3/1959 Klotz et al. .
3,488,418 1/1970 Holliday et al. .
3,524,910 8/1970 Holliday et al. .
3,882,228 5/1975 Bonney et al. .
4,016,254 4/1977 Seager .
4,017,598 4/1977 Ohno et al. .
4,371,516 2/1983 Gregory et al. .
4,547,359 10/1985 Zicrenberg et al. .
4,574,080 3/1986 Roswall et al. .
4,666,703 5/1997 Kopf .
4,687,662 8/1987 Schobel .
4,710,384 12/1987 Rotman .
4,760,093 7/1988 Blank et al. .
4,832,956 5/1989 Gergely et al. .
4,851,226 7/1989 Julian et al. .
4,867,987 9/1989 Seth .
4,874,614 10/1989 Becker .
4,886,669 12/1989 Ventouras .
4,904,477 2/1990 Ho et al. .
4,915,953 4/1990 Jordan et al. .
4,940,588 7/1990 Sparks et al. .
5,047,247 9/1991 Milovac et al. .
5,073,374 12/1991 McCarty et al. .
5,073,377 12/1991 Alexander et al. .
5,178,878 1/1993 Wehling et al. .
5,198,228 3/1993 Urban et al. .
5,215,756 6/1993 Cole et al. .
5,464,632 11/1995 Cousin et al. .
5,576,014 11/1996 Mizumoto et al. .
5,629,016 5/1997 Fieldman et al. .

FOREIGN PATENT DOCUMENTS

49161/85 10/1985 Australia .
79507/87 10/1987 Australia .

33946/89 5/1989 Australia .
66012/90 9/1990 Australia .
72560/91 2/1991 Australia .
052076 B1 of 0000 European Pat. Off. .
250648 A2A3 of 0000 European Pat. Off. .
003589 A2 2/1979 European Pat. Off. .
196546 A2 2/1979 European Pat. Off. .
207041 A2 6/1986 European Pat. Off. .
255002 A1 7/1987 European Pat. Off. .
266113 10/1987 European Pat. Off. .
273005 A1 11/1987 European Pat. Off. .
281200 A1 2/1988 European Pat. Off. .
313328 A1 10/1988 European Pat. Off. .
347767 A1 6/1989 European Pat. Off. .
350701 6/1989 European Pat. Off. .
408273 A1 7/1990 European Pat. Off. .
1134097 1/1968 United Kingdom .
154022 7/1979 United Kingdom .
2067900 1/1980 United Kingdom .
2086725 8/1985 United Kingdom .
2087235 11/1990 United Kingdom .
WO91/04757 4/1991 WIPO .
WO91/16043 10/1991 WIPO .

OTHER PUBLICATIONS

Lehman, K., "Formulation of Controlled Release Tablets
with Acrylic Resins" Acta. Pharma. Penn. 93, pp. 55-74
(1984).

Lehman, K.O.R., "Chemistry & Application Properties of
Polymethacrylate Coating Systems" in Aqueous Polymeric
Coatings for Pharmaceutical Dosage Forms (J.W. McGinity,
ed.) pp. 222-234, Marcel Dekker Inc., New York (1989).

(List continued on next page.)

Primary Examiner—Thurman K. Pogo
Assistant Examiner—Brian K. Seidleck
Attorney, Agent, or Firm—Caesar, Rivise, Bernstein, Cohen
& Pokotilow, Ltd.

[57] ABSTRACT

The invention relates to a rapidly disintegratable multipar-
ticulate tablet which disintegrates in the mouth in less than
40 seconds and which comprises an excipient and an active
ingredient in the form of microcrystals coated with a coating
agent. The excipient comprises, with respect to the mass of
the tablet, from 3 to 15% by weight of at least one disinte-
gration agent and from 40 to 90% by weight of at least one
soluble diluent agent with binding properties consisting of a
polyol having less than 13 carbon atoms, said polyol being
either in the directly compressible form which is composed
of particles whose average diameter is from 100 to 500
micrometers or in the powder form which is composed of
particles whose average diameter is less than 100
micrometers, said polyol being selected from the group
consisting of mannitol, xylitol, sorbitol and maltitol, with
the proviso that, when only one soluble diluent agent with
binding properties is used, it is a polyol in the directly
compressible form except sorbitol and, when at least two
soluble diluent agents with binding properties are used, one
is consisting of a polyol in the directly compressible form
and the other is consisting of the same or another polyol in
powder form, the proportion of directly compressible polyol
to powder polyol being from 99/1 to 50/50.

12 Claims, No Drawings

OTHER PUBLICATIONS

Butterworth's Medical Dictionary, 2nd Edition (1978) Butterworths, London, ISBN 0 407 00193 X; p. 1449.
Remington's Pharmaceutical Sciences, 18th Edition (1990) "Disintegrants", Mack Publishing Co, ISBN 0-912734-04-3, p. 1637.
Remington's Pharmaceutical Sciences, Mack Publishing Co. pp. 1604-1605 (1975).
Pharmaceutical Dosage Forms, vol. 1, ed. Lieberman & Lachman, Marcel Dekker, Inc., ISBN 0-8247-6918-X (1980), pp. 72-88, 135-136, 289-294.
Pharmaceutical Dosage Forms, vol. 1, ed. Lieberman & Lachman, Marcel Dekker, Inc., ISBN 0-8247-6918-X (1980), pp. 135-141.
J. Putter, Med. Welt, Bd. 27/Heft 28, pp. 1362-1365 (1976) (and English Translation).
Rote Liste 1982, 78 002 (and English Translation).
Beipackzettel Colfarit, Sep. 1987 (and English Translation).
Auszug aus der Herstellungsvorschrift für Colfarit, gültig ab Jun. 19, 1990 with the abstract Apr. 4, 1991 gültigen Zefallstest (and English Translation).
"Tablettieren" "verpressen von überzogenen Partikeln zu zerfallenden Tabletten mit kontrollierter Wirkstoffabgabe" of 09.05-11.05-1990 (and English Translation).
Duchene, D. "Tablet disintegration" in Topics in Pharmaceutical Sciences, (1983), (D.D. Bremer and P. Spoiser, eds) p. 387-399, Elsevier Science Publishers, Amsterdam, New York and Oxford (and English Translation).
NYMCEL brochure, 6 pages, undated.
The Theory & Practice of Industrial Pharmacy, Lea & Febiger, pp. 320-321, , 325-328, 412-429 (1986).
Merck Index, pp. 6, 114, 156, 247, 248, 649 1109 (1976).
Article Pharm. Ind. 48, Saki, p. 92-94 (1986).
Manufacturing Chemist and Aerosol News, Apr. 1977, Seager, pp. 25-35.
Manufacturing Chemist, Mar. 1982, pp. 31-33, Lang.
International Journal of Pharmaceutics, 41, 159-167, Wan (1980).
Pharm. Dosage Forms vol. 1, Chap. 2 pp. 86-88, Lieberman (1980).
Pharm. Dosage Forms vol. 1, Chap. 3 pp 135-141, Lieberman (1980).

Chemical Technology Review No. 73, Gutcho (1976).
J. Pharmaceut. Sci., 68, 206-211 Lerk et al. (1979).
Ed. Marcel Dekker, Inc., New York pp. 359-403, Marshall (1979).
Amer. Pharm. Assoc. and the Pharm. Society of Great Britain pp. 369-375, Handbook of Pharm. Excip. (1986).
Manuf. Chemist & Aerosol News, Jan. 1976 pp. 25-26, Khan.
Congress of Pharm. Sciences Sept. 5-9, 1983, pp. 387-399 "Tablet disintegration", Duchene.
Ed. Marcel Dekker, New York (1989) pp. 153-245, Lieberman.
Ed. Marcel Dekker, New York pp. 1-33, 161-179, 279-287, Deasy (1984).
Chem. Technology Rev. No. 135, Gutcho (1979).
Microencapsulation: Processes and Applications, Vandegær (1974).
Microencapsulation, Drugs, and the Pharm. Sciences, vol. 3, Nixon (1976).
Pharm. Technology—Controlled Drug Release, vol. 2 p. 152-152, Oracecka (1991).
Pharm. Dosage Forms vol. 1, Chapter 8, p. 372-376, Lieberman (1989).
Pharm. Dosage Forms, vol. 3, pp. 110 and 157-164, Lieberman (1982).
Pharm. Dosage Forms, vol. 1, pp. 284-286, Lieberman.
Pharm. Dosage Forms, vol. 2, pp. 219-220, Lieberman (1990).
Chem. Pharm. Bull 38(3), 752-756, Yuasa (1990).
Drug. Devel. and Ind. Pharmacy, 12(4), p. 577-587, Abdel Monem Sayed (1986).
Journ. of Pharm. Sc., 73 (Jan) pp. 52-54, Nixon (1984).
Journ. of Pharmacy and Pharmacology, 29 (Mar), pp. 169-173, Jalsenjak (1977).
Journ. of Pharmacy and Pharmacology, 32, pp. 678-680, Jalsenjak (1980).
Acta Pharm. Fenn, 93, 55, Seminar 7 (Feb. 1984).
Drug Devel. and Ind. Pharmacy, 15, 2049-2053, Prapaitrakul (1989).
Pharm. Pelletization Technology (1989) pp. 1-11, 86-105, 187-215.

1

MULTIPARTICULATE TABLET DISINTEGRATING IN LESS THAN 40 SECONDS IN THE MOUTH

The invention relates to an improved rapidly disintegratable multiparticulate tablet of the type which disintegrates in the mouth in less than 40 seconds and which comprises, on the one hand, an active ingredient in the form of microcrystals coated with a coating agent and, on the other hand, an excipient.

The active ingredient may be selected from the group comprising analgesics, antipyretics, antidiarrheals, antispasmodics, digestive motoricity regulators and anti-inflammatories and more particularly from the group comprising paracetamol, ibuprofen, aspirin, ketoprofen and loperamide.

French Patent FR 91 09245 discloses multiparticulate tablets of the type in question which are generally satisfactory; however, the texture of some of these tablets leads to a gritty and pasty sensation on ingestion.

The object of the invention is above all to overcome this drawback and to supply a rapidly disintegratable tablet with a systematically pleasant texture, this tablet also leading to an optimum biological availability of the active ingredient.

The Applicants have had the merit of discovering, following extensive research, that this object could be achieved on the one hand by incorporating into the excipient a disintegration agent and at least one particular soluble diluent agent with binding properties and, on the other hand, by selecting the coating agent as a function of the physico-chemical characteristics of the active ingredient.

As a result, the improved multiparticulate tablet according to the invention, which disintegrates in the mouth in less than 40 seconds and which comprises, on the one hand, an active ingredient in the form of coated microcrystals and, on the other hand, an excipient, is characterized in that

the excipient comprises at least one disintegration agent and at least one soluble diluent agent with binding properties consisting of a polyol having less than 13 carbon atoms either in the form of the directly compressible product with an average particle diameter of between 100 and 500 micrometres, or in the form of a powder the average particle diameter of which is less than 100 micrometres, this polyol preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being understood that sorbitol cannot be used alone and that, when there is a single soluble diluent agent with binding properties, it is used in the form of the directly compressible product whereas, when there are at least two soluble diluent agents with binding properties, one is in the directly compressible form and the other in the form of a powder, it being then possible that the polyol is the same, the proportion of directly compressible polyol to powder polyol being from 99/1 to 50/50 and preferably from 80/20 to 50/50 and

the coating of the microcrystals of active ingredient comprises at least one coating agent selected, as a function of the physico-chemical characteristics of the active ingredient, from the group comprising polymethacrylates, cellulose polymers, in particular ethyl celluloses, hydroxypropyl-methyl celluloses, hydroxypropyl celluloses and cellulose acetophthalates and combinations of these polymers with each other optionally combined with plastifiers or soluble agents, in particular polyols.

The invention will be better understood using the additional description and non-limitative examples relating to advantageous methods of implementation which follow.

2

With the intention of preparing a multiparticulate tablet of the type in question, the procedure is as follows or in an equivalent fashion.

First the active ingredient is selected from the group comprising analgesics, antipyretics, antidiarrheals, antispasmodics, digestive motoricity regulators and anti-inflammatories and more particularly from the group comprising paracetamol, ibuprofen, aspirin, ketoprofen and loperamide.

The excipient is prepared by mixing at least one disintegration agent with at least one soluble diluent agent with binding properties consisting of a polyol having less than 13 carbon atoms either in the form of a directly compressible product the average particle diameter of which is from 100 to 500 micrometres or in the form of a powder the average particle diameter of which is less than 100 micrometres, this polyol preferably being selected from the group comprising mannitol, xylitol, sorbitol and maltitol, it being understood that sorbitol cannot be used alone.

When there is a single soluble diluent agent with binding properties, therefore different from sorbitol, it is used in the form of a directly compressible product.

When at least two soluble diluent agents with binding properties are used, one is present in the form of the directly compressible product and the other, which can be the same polyol, is in the form of a powder the average component particle diameter of which is less than 100 micrometres, the proportion of directly compressible polyol to powder polyol being from 99/1 to 50/50 and preferably from 80/20 to 50/50.

The disintegration agent is preferably selected from the group comprising cross-linked polyvinylpyrrolidone, designated in the art by the term crospovidone and cross-linked sodium carboxymethylcellulose designated in the art by the term sodium croscarmellose.

The respective proportions of disintegration agent and binding agent or soluble diluent used for the constitution of the excipient are, with respect to the mass of the tablet, from 3 to 15% by weight, preferably from 5 to 10% by weight for the first and from 40 to 90% by weight, preferably from 50 to 70% by weight for the second; the maximum proportion of sorbitol is 30% by weight.

The active ingredient which is a component of the composition of the tablet according to the invention is presented before coating in the form of microcrystals the average diameter of which is from approximately 1 to approximately 500 micrometres.

In the case of certain active ingredients, microcrystals with an average diameter of less than 100 micrometres are preferably used in order to increase the exchange surface between the active ingredient and the ambient environment; by proceeding in this way, the solubilization speed and/or the intrinsic solubility of dissolution are optimized.

The microcrystals are preferably coated using the technique known as the fluidized bed.

Direct coating is applied in the case of microcrystals having an average size of 100 to 500 micrometres; for microcrystals smaller than 100 micrometres, a prior treatment is carried out consisting either in the granulation of the microcrystals by a standard wet or dry granulation process, or by prior fixing of the microcrystals on neutral supports known in themselves when the average size of said microcrystals is less than approximately 20 micrometres; the microcrystals are fixed to the neutral supports in a standard manner using a binding agent consisting for example of hydroxypropylmethyl cellulose.

The coating is obtained from at least one coating agent selected, according to the physico-chemical characteristics

of the active ingredient, from the group comprising the polymethacrylates, in particular certain of those marketed under the EUDRAGIT trade mark and more particularly the 30% dispersions of poly(ethylacrylate-methyl-metacrylate) marketed under the trade mark EUDRAGIT NE 30 D, the type E aminoalkyl-methacrylate copolymers marketed under the trade mark EUDRAGIT E, the cellulose polymers, in particular the ethyl celluloses, hydroxypropyl-methyl celluloses, hydroxypropyl celluloses and the cellulose acetophthalate, the combinations of these polymers with each other and optionally in association with plastifiers, for example polyethyleneglycol 6000, or with soluble agents, in particular polyols, for example mannitol.

As an example, the coating can be constituted starting from

- EUDRAGIT NE 30 D alone or mixed with EUDRAGIT E in one or more organic solvents,
- ethyl cellulose alone or mixed with hydroxypropyl-methyl cellulose in association with a plastifier optionally in the presence of a hydroalcoholic solvent,
- a polymethacrylate, in particular EUDRAGIT NE 30 D mixed with a soluble cellulose derivative, in particular hydroxypropyl-methyl cellulose and a plastifier and/or a soluble diluent agent with binding properties,
- EUDRAGIT E 100 alone.

Due to the coating according to the invention of the microcrystals of active ingredient, said coating comprising in particular a in association or combination a soluble polymer and an insoluble polymer, the definitive tablet is characterized in that

on the one hand, in an acid medium with a pH lower than 5, the quantity of active ingredient which is dissolved, after disintegration of the tablet, in 5 to 20 minutes from the coated microcrystals is equal to at least 80% and preferably to at least 100% of the quantity of active ingredient which is dissolved in the same time period following disintegration from a tablet allowing the immediate release of the active ingredient consisting of microcrystals but in which said microcrystals are not coated and,

on the other hand, the active ingredient does not dissolve significantly after remaining for a period of less than 5 minutes in a medium the pH conditions of which are similar to those of saliva, namely 7.0 ± 0.5 , thus ensuring satisfactory masking of its taste.

When the quantity of active ingredient which is dissolved after disintegration of the tablet in 5 to 20 minutes from the coated microcrystals is equal to at least 100% of the quantity of active ingredient which is dissolved in the same time period after disintegration from a tablet allowing the immediate release of the active ingredient consisting of microcrystals but in which said microcrystals are not coated, the biological availability of the active ingredient is at least equivalent to that of the same active ingredient obtained from the above tablet in which said microcrystals are not coated.

For the production of the tablet, a mixture of the excipient and the coated microcrystals is first prepared and this mixture is then homogenized in a dry mixer.

Preferably, a sweetener, a flavouring and a lubricant are incorporated to this mixture.

The sweetener can be selected from the group comprising Aspartame and sodium saccharinate, and the lubricant from the group comprising magnesium stearate, sodium stearyl fumarate, stearic acid and polyethyleneglycol 6000.

The mixture is then subjected to a compression force sufficient to confer on the resulting tablet a sufficient hard-

ness for it to be handled and packaged industrially, then carried and handled by the patient without any particular precautions; for information only, it is indicated that the hardnesses meeting these conditions are generally comprised between 20 and 70 Newtons.

The tablets according to the invention present, with respect to the tablets of the type in question which already exist, simultaneously an improvement in the speed at which the active ingredient is made available in the organism and an improvement in palatability.

EXAMPLE 1

Multiparticulate paracetamol tablet dosed at 500 mg. The composition of the above tablet results from Table I below.

TABLE I

Constituents	Content in formula
Coated paracetamol	39.2
Mannitol for direct compression	36.7
Crystalline powder mannitol	12.3
Croscopolone	8.6
Aspartame	2.7
Blackcurrant flavouring	0.4
Magnesium stearate	0.1
Total	100.0%

This tablet is prepared as indicated below.

The paracetamol microcrystals are introduced into a fluidized bed installation and a dispersion in ethanol of EUDRAGIT E 100, EUDRAGIT NE 30 D and colloidal silica is sprayed onto the microcrystals in order to obtain microcrystals coated with 10% of polymer.

All the excipients are sieved and the mixture containing the coated paracetamol and the excipients is homogenized in a dry mixer.

The mixture is divided and moulded on a tableting machine equipped with 17 mm diameter punches.

The compression force is adjusted in order to obtain tablets having a hardness of 40 ± 10 Newtons.

The disintegration time in the mouth of the tablets thus obtained is less than 40 seconds.

This time corresponds to the time which separates, on the one hand, the moment the tablet is placed in contact with the saliva in the mouth and, on the other hand, the moment the suspension, resulting from the disintegration of the tablet in contact with the saliva, is swallowed.

The disintegration time less than 40 seconds indicated above is the average of the values noted for a representative group of healthy subjects.

The pharmacokinetic study to which the above tablet was subjected shows that the biological availability of the active ingredient, namely paracetamol, is not significantly different from that which is observed after administration of a commercially available tablet based on paracetamol. The masking of the taste of the paracetamol by the coating present on the tablet according to the invention does not therefore result in any delay in absorption, which is even slightly more rapid as the maximum is achieved in 0.5 hour on average whereas it is only achieved in 0.88 hour on average in the case of the commercially available reference tablet.

The values recorded with respect to the properties of the tablet according to the invention and those relating to a currently marketed paracetamol-based tablet with immediate release of the active ingredient and not previously coated are shown in Table II below.

TABLE II

Parameter	Tablet containing a 500 mg dose of paracetamol according to the invention	Commercially available tablet containing a 500 mg dose of paracetamol
Lag t (h)	0.17	0.17
t _{max} (h)	0.50	0.88
C _{max} (µg/ml)	6.28 ± 1.61	6.26 ± 2.37
AUC _{0-t} (µg · h/ml)	18.59 ± 3.44	18.10 ± 3.40
AUC _{inf} (µg · h/ml)	19.68 ± 3.85	19.24 ± 3.79

In this table, lag t designates the time in hours which elapsed between the administration of the medicament and the detection of the active ingredient in the subject's blood, t_{max} designates the time in hours after which the serum concentration of active ingredient reaches a maximum, C_{max} (µg/ml) designates the value of the maximum concentration of active ingredient reached at the value t_{max}; this concentration is expressed in µg of active ingredient per ml of serum, AUC_{0-t} designates the surface area under the curve of the serum concentrations of active ingredient as a function of time until the last quantified sample is taken, and AUC_{inf} designates the surface area under the curve of the serum concentrations of active ingredient as a function of time extrapolated to infinity.

An examination of the results shown in Table II shows that the coating used to mask the taste of the active ingredient does not result in a modification of the biological availability of the active ingredient or any delay in absorption, which is a determining result in the administration of certain active ingredients where rapid action is desired, in particular analgesics.

EXAMPLE 2

Multiparticulate loperamide tablet at a dose of 2 mg.
The composition of the above tablet results from Table III below.

TABLE III

Constituents	Centesimal formula
Coated loperamide	15.1
Mannitol for direct compression	56.6
Crystalline powder mannitol	18.8
Crospovidone	5.0
Aspartame	3.0
Mint flavouring	0.7
Magnesium stearate	0.8
Total	100.0%

This tablet is prepared in the manner indicated in Example 1.

The active ingredient is presented in the form of microcrystals the average size of which is less than 20 micrometres; consequently, fixing of these microcrystals on neutral supports consisting of a polyol and having an average size of the order of 60 micrometres is carried out using a hydroxypropyl-methyl cellulose solution.

The neutral supports comprising the loperamide microcrystals are then coated with 20% of a mixture of EUDRAGIT NE 30 D and EUDRAGIT E 100.

This tablet has a hardness of 30±5 Newtons.
It disintegrates in the mouth in 20 seconds.

EXAMPLE 3

Ketoprofen tablet at a dose of 12.5 mg.
The composition of the above tablet results from Table IV below.

TABLE IV

Constituents	Centesimal formula
Coated ketoprofen	6.7
Mannitol for direct compression	63.3
Crystalline powder mannitol	22.2
Crospovidone	5.0
Aspartame	1.3
Mint flavouring	0.7
Magnesium stearate	0.8
Total	100.0%

It is prepared in the manner indicated in Example 2.

The active ingredient is presented in the form of microcrystals the average size of which is less than 20 micrometres; consequently, fixing of these microcrystals on neutral supports consisting of a polyol and the size of which is of the order of 60 micrometres is carried out using a hydroxypropyl-methyl cellulose solution.

The neutral supports comprising the ketoprofen microcrystals constituting the above tablet are then coated with 20% of a mixture of EUDRAGIT NE 30 D, hydroxypropyl-methyl cellulose and polyethylene-glycol 6000.

It has a hardness of 35±5 Newtons.
It disintegrates in the mouth in 20 seconds.

EXAMPLE 4

Multiparticulate acetylsalicylic acid tablet at a dose of 325 mg.
The composition of the above tablet results from Table V below.

TABLE V

Constituents	Centesimal formula
Coated acetylsalicylic acid	37.4
Mannitol for direct compression	38.0
Crystalline powder mannitol	12.6
Crospovidone	8.6
Aspartame	2.9
Sodium stearyl fumarate	0.5
Total	100.0%

This tablet is prepared in the manner indicated in Example 1.

The acetylsalicylic acid microcrystals constituting the above tablet are coated with 4.5% of ethyl cellulose N7 and polyethyleneglycol 6000.

The tablet has a hardness of 50±15 Newtons.
It disintegrates in the mouth in 20 seconds.

EXAMPLE 5

Multiparticulate ibuprofen tablet at a dose of 100 mg.
The composition of the above tablet results from Table VI below.

TABLE VI

Constituents	Centesimal formula
Coated ibuprofen	14.4
Mannitol for direct compression	52.5
Crystalline powder mannitol	17.5
Croscavolone	10.0
Aspartams	3.7
Cherry flavouring	0.9
Magnesium stearate	1.0
Total	100.0%

This tablet is prepared in the manner indicated in Example 1.

The ibuprofen microcrystals having an average size in the region of 30 micrometres are granulated by a standard wet route granulation process. The resulting particle is then coated with 20% of a mixture of ethyl cellulose N7 and polyethyleneglycol 6000.

The resulting coated ibuprofen crystals are mixed with the excipient, then subjected to compression.

The resulting tablet has a hardness of 40±10 Newtons. It disintegrates in the mouth in 30 seconds.

What is claimed is:

1. A multiparticulate tablet disintegrating in the mouth in less than 40 seconds and comprising an excipient and an active ingredient in the form of microcrystals comprising a taste-making coating wherein

the excipient comprises, with respect to the mass of the tablet, from 3 to 15% by weight of at least one disintegration agent selected from the group consisting of cross-linked polyvinylpyrrolidone and cross-linked carboxymethylcellulose and from 40 to 90% by weight of at least one soluble diluent agent with binding properties consisting of a polyol having less than 13 carbon atoms, said polyol being either in the directly compressible form which is composed of particles whose average diameter is from 100 to 500 micrometers or in the powder form which is composed of particles whose average diameter is less than 100 micrometers, said polyol being selected from the group consisting of mannitol, xylitol, sorbitol and maltitol, with the proviso that, when only one soluble diluent agent with binding properties is used, it is a polyol in the directly compressible form except sorbitol and, when at least two soluble diluent agents with binding properties are used, these are consisting of the same polyol, one part of which is in the directly compressible form while the other part is in powder form, the proportion of directly compressible polyol to powder polyol being from 99/1 to 50/50 and

the coating of the microcrystals of active ingredient comprises at least one coating agent selected as a function of the physico-chemical characteristics of the

active ingredient selected from the group consisting of polymethacrylates and cellulose polymers and combinations thereof with each other.

2. A multiparticulate tablet according to claim 1, wherein the proportion of disintegrating agent and of soluble diluent agent with binding properties is respectively from 5 to 10% and from 50 to 70% by weight.

3. A multiparticulate tablet according to one of claim 1 or 2, wherein the maximum proportion of sorbitol is 30% by weight.

4. A multiparticulate tablet according to claim 1, wherein the proportion of directly compressible polyol to powder polyol is from 80/20 to 50/50.

5. A multiparticulate tablet according to claim 1, wherein the coating agent is selected from the group consisting of hydroxypropyl-methyl cellulose, hydroxypropyl cellulose and cellulose acetophthalates.

6. A multiparticulate tablet according to claim 1, wherein the coating agent is combined with at least one of the products of the group consisting of plasticizers, soluble agents and polyols.

7. A multiparticulate tablet according to claim 1, wherein the bioavailability of the active ingredient is at least equivalent to that of the active ingredient of the same tablet wherein the said active ingredient is not coated, allowing thus its immediate release.

8. A multiparticulate tablet according to claim 7, wherein the quantity of active ingredient which is dissolved from the coated microcrystals, after disintegration of the tablet, in 5 to 20 minutes when placed in an acid medium having a pH lower than 5, is equal to at least 80% of the quantity of active ingredient which is dissolved in the same time after disintegration from a tablet which is identical except the fact that the microcrystals are not coated.

9. A multiparticulate tablet according to claim 7, wherein the quantity of active ingredient which is dissolved from the coated microcrystals, after disintegration of the tablet, in 5 to 20 minutes when placed in an acid medium having a pH lower than 5, is equal to at least 100% of the quantity of active ingredient which is dissolved in the same time after disintegration from a tablet which is identical except the fact that the microcrystals are not coated.

10. A multiparticulate tablet according to one of claims 7 to 9, wherein the active ingredient does not dissolve significantly after remaining for a period of less than 5 minutes in a medium the pH conditions of which is 7.0±0.5, thus providing satisfactory masking of the taste.

11. A multiparticulate tablet according to claim 1, wherein the active ingredient is selected from the group consisting of analgesics, antipyretics, antidiarrheals, antispasmodics, digestive motoricity regulators and anti-inflammatories.

12. A multiparticulate tablet according to claim 1, wherein the active ingredient is selected from the group consisting of paracetamol, ibuprofen, aspirin, ketoprofen and loperamide.

* * * * *

163 68
D3



US006024981A

United States Patent [19]
Khankari et al.

[11] **Patent Number:** 6,024,981
[45] **Date of Patent:** Feb. 15, 2000

[54] **RAPIDLY DISSOLVING ROBUST DOSAGE FORM**

[75] **Inventors:** Rajendra K. Khankari, Maple Grove;
John Hontz, Plymouth; Sara J.
Chastain, Maple Grove; Leo Katzmer,
Eden Prairie, all of Minn.

[73] **Assignee:** Cima Labs Inc., Eden Prairie, Minn.

[21] **Appl. No.:** 09/057,884

[22] **Filed:** Apr. 9, 1998

Related U.S. Application Data

[60] **Provisional application No.** 60/043,242, Apr. 16, 1997.

[51] **Int. Cl.⁷** A61K 9/14; A61K 9/18;
A61K 9/20; A61K 9/22; A61K 9/26

[52] **U.S. CL** 424/464; 424/465; 424/468;
424/469; 424/470; 424/484; 424/488; 424/489;
424/490; 424/435; 514/777; 514/951; 514/960

[58] **Field of Search** 424/464, 465,
424/468, 469, 470, 484, 488, 489, 490,
441, 435

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,962,417 6/1976 Howell 424/52

4,613,497	9/1986	Chavkin	424/44
4,639,368	1/1987	Niaz et al.	424/48
4,687,662	8/1987	Schobel	424/44
4,753,792	6/1988	Aberg	424/44
4,940,588	7/1990	Sparks et al.	424/490
5,055,306	10/1991	Barry et al.	424/482
5,178,878	1/1993	Wehling et al.	424/466
5,225,197	7/1993	Bolt et al.	424/440
5,464,632	11/1995	Coulin et al.	424/465
5,536,526	7/1996	Virtanen et al.	426/658
5,607,697	3/1997	Alkire et al.	424/495

OTHER PUBLICATIONS

U.S. Pharmacopocia No. 23, 1995, Chap. 1216, "Tablet Friability".

Primary Examiner—James M. Spear
Attorney, Agent, or Firm—Lorner, David, Littenberg,
Krumholtz & Montlik, LLP

[57] **ABSTRACT**

The invention is directed to a hard tablet that can be stored, packaged and processed in bulk. Yet the tablet dissolves rapidly in the mouth of the patient with a minimum of grit. The tablet is created from an active ingredient mixed into a matrix of a non-direct compression filler and a relatively high lubricant content.

40 Claims, No Drawings

RAPIDLY DISSOLVING ROBUST DOSAGE FORM

This application claims the benefit of Provisional Application Ser. No. 60/043,242 filed Apr. 16, 1997.

FIELD OF THE INVENTION

The present invention relates to the pharmaceutical industry, the medical industry, and, in particular, to the creation of dosage forms.

BACKGROUND OF THE INVENTION

It is known to produce an in-mouth disintegrable dosage form for the delivery of drugs. In fact, patents relating generally to this area date back to the last century. Such tablets have significant advantages over other dosage forms; particularly for those who cannot, or will not, swallow a tablet or capsule. Solid dosage forms are far more convenient than liquids. However, the design of orally disintegrable dosage forms carries with it its own set of unique problems.

Chewable tablets such as, for example, those disclosed in U.S. Pat. No. 5,225,197 to Bolt, can be provided. However, such dosage forms often provide inadequate taste-masking of bad tasting medicaments. Chewable formulations are also often incompatible with, for example, delicate microparticles or time-released microparticles. The compressive force used in forming tablets and/or during chewing will often rupture such structures either exposing the patient to the objectionable taste of the material contained therein, or interfering with the structural integrity of the encapsulant and thereby altering its drug delivery profile.

Non-chewable dosage forms have also been tried. For example, Cima Labs has produced oral dosage forms including microparticles and effervescent which rapidly disintegrate in the mouth and provide adequate taste-masking. See Wehling et al., U.S. Pat. No. 5,178,878. Zydis, on the other hand, produces a rapidly dissolvable, freeze-dried, sugar matrix to produce a rapidly dissolving tablet. While these dosage forms are effective, they provide significant problems in terms of production, storage, transport and during consumer usage. They are also significantly more costly to produce.

According to U.S. Pharmacopoeia No. 23, 1995, Chap. 1216 entitled "Tablet Friability," the text of which is hereby incorporated by reference, effervescent tablets and chewable tablets often have different specifications as far as friability, when compared to normal tablets. These tablets normally require special packaging. That, however, is a great understatement.

The Zydis tablets, for example, are so fragile that the matrix material must be formed by freeze-drying in an individual tablet-sized container. While the use of an effervescent couple in combination with microparticles as disclosed in Wehling et al. does overcome the need for such extreme measures, the need to minimize in-mouth disintegration times still require the use of non-traditional packaging and processing methodology. For example, normal conveyors such as vibratory conveyors or bulk hoppers common in the pharmaceutical industry could not be used, as these high-speed, high-volume devices tend to cause damage to the resulting tablets. Similarly, the resulting tablets cannot be stored on a hopper after tableting but before packaging. This can seriously interfere with the processing efficiencies of high-volume presses.

Moreover, the resulting tablets have to be packaged in individual, blister-type packages that are robust enough to

avoid tablet breakage. They could not be packaged in a conventional, multi-tablet bottle, individual foil pouches or traditional blister packaging.

SUMMARY OF THE INVENTION

The present invention relates to a hard, compressed, rapidly dissolvable dosage form adapted for direct oral dosing. The dosage form includes an active ingredient and a matrix. The matrix is composed of at least a non-direct compression filler and a lubricant. The dosage form is adapted to rapidly dissolve in the mouth of a patient and thereby liberate the active ingredient. Preferably, the dosage form has a friability of about 2% or less when tested according to the U.S.P. The dosage form also preferably has a hardness of 15-50 Newtons ("N").

It is desirable that the dosage form dissolve in about 90 seconds or less in the patient's mouth. It is also often desirable that the dosage form include at least one particle. The particle would be the active ingredient and a protective material. These particles can include rapid release particles and or sustained release particles.

In a particularly preferred formulation in accordance with the present invention there is provided a hard, compressed, rapidly dissolving tablet adapted for direct oral dosing. The tablet includes particles made of an active ingredient and a protective material. These particles are provided in an amount of between about 0.01 and about 75% by weight based on the weight of the tablet. The tablet also includes a matrix made from a non-direct compression filler, a wicking agent, and a hydrophobic lubricant. The tablet matrix comprises at least about 60% rapidly water soluble ingredients based on the total weight of the matrix material. The tablet has a hardness of between about 15 and about 50 Newtons, a friability of less than 2% when measured by U.S.P. and is adapted to dissolve spontaneously in the mouth of a patient in less than about 60 seconds and thereby liberate said particles and be capable of being stored in bulk.

The dosage forms described above are able to dissolve rapidly in the mouth of the patient, with a minimum of grit or other organoleptically unpleasant species. Moreover, because the dosage forms are hard and have low friability they can be handled and packaged like other, non-rapidly dissolving dosage forms.

Therefore, in another aspect of the present invention, there is provided a method of making a packaged, orally dissolvable dosage form. The method includes the steps of:

- (a) forming a mixture including an active ingredient and a matrix including a non-direct compression filler and a lubricant;
- (b) compressing the mixture to form a plurality of hard, compressed, rapidly disintegrable dosage forms including the active ingredient distributed in the orally dissolvable matrix; and
- (c) storing the dosage forms in bulk prior to packaging. In a preferred embodiment, the dosage forms are then packaged in a lumen of a package such that there is at least one per package. In a preferred particularly preferred embodiment, the dosage forms are then packaged in a lumen of a package such that there more than one per package. Direct compression is the preferred method of forming the dosage forms.

There is also provided hereby an openable and recloseable package containing a plurality of hard, compressed, rapidly dissolving tablets adapted for direct oral dosing as described above.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

The present invention is directed to a hard, compressed, rapidly dissolvable dosage form adapted for direct oral

69
164

dosing. The dosage form includes an active ingredient often in the form of a protected particle, and a matrix. The matrix includes a non-direct compression filler and a lubricant, although, it may include other ingredients as well. The dosage form is adapted to rapidly dissolve in the mouth of a patient. Yet, it has a friability of about 2% or less when tested according to the U.S.P. Generally, the dosage form will also have a hardness of at least about 15-20 Newtons. Not only does the dosage form dissolve quickly, it does so in a way that provides a positive organoleptic sensation to the patient. In particular, the dosage form dissolves with a minimum of unpleasant grit which is tactilely very inconsistent with organoleptic sensation of the dosage form.

"Dosage form," in accordance with the present invention, includes tablets and "slugged cores" used in capsules or caplets (a hybrid tablet/capsule). "Dissolvable," should be understood as describing the action of the dosage form as it is held in the mouth. In this case, the dosage form gets continuously smaller in a process which is conceptually analogous to melting. While the dosage form may also disintegrate into smaller pieces to some extent, particularly where a relatively greater amount of a wicking agent or effervescent disintegrant is used, or where the dosage form is chewed, that is not its principal mechanism. The majority of the matrix material actually dissolves into the saliva while the tablet is in the patients mouth. Ideally, before a patient actually swallows the tablet, substantially all of the rapidly water soluble components of the matrix have actually dissolved. Moreover, the amount of rapidly water soluble ingredients in each dosage form is maximized in accordance with the present invention. In this way, as well as in others as described herein, dosage forms in accordance with the present invention are distinguishable from the disintegrable tablets commonly described in the prior art, such as those described in, for example, those of Cousins et al., U.S. Pat. No. 5,464,632. "Rapidly dissolve(able)" means that the rapidly water soluble ingredients will dissolve sufficiently to allow ingestion as a non-gritty solution or slurry in 90 seconds or less, preferably 60 seconds or less and most preferably 45 seconds or less. The rapid dissolution of the dosage form, as well as its composition are designed to minimize the gritty, sandy feel of conventional disintegrable tablets. By minimizing the degree of disintegration during the dissolution of the dosage form, one can avoid adding to the unpleasant organoleptic sensation of grit.

"Water soluble" in accordance with the present invention has its usual meaning. However, "rapidly water soluble" means that the ingredient in question will dissolve in a time frame which is consistent with the objects of the invention. For example, a very fine grained or powdered sugar known as a non-direct compression sugar may be used as a filler in the matrix of the present invention. This material, in part because of its chemical composition and in part because of its fine particle size, will dissolve readily in the mouth in a matter of seconds once it is wetted by saliva. Not only does this mean that it can contribute to the speed at which the dosage form will dissolve, it also means that while the patient is holding the dissolving dosage form in his or her mouth, the filler will not contribute a "gritty" or "sandy" texture thus adversely affecting the organoleptic sensation of taking the dosage form. In contrast, direct compression versions of the same sugar are usually granulated and treated to make them larger and better for compaction. While these sugars are water soluble, they may not be solubilized quickly enough. As a result, they can contribute to the gritty or sandy texture of the dosage form as it dissolves. Dissolution time in the mouth can be measured by observing the dissolution

time of the tablet in water at about 37° C. The tablet is immersed in the water without forcible agitation or with minimal agitation. The dissolution time is the time from immersion to substantially complete dissolution of the rapidly water soluble ingredients of the tablet as determined by visual observation.

To further improve the organoleptic qualities of the dosage forms of the present invention, the amount of non-rapidly dissolvable, i.e., non-rapidly water soluble materials used is minimized as much as possible. Ideally, the only non-rapidly dissolving species would be the active ingredient, particularly when in protected particle form, and the lubricant. The use of a rapidly water soluble active ingredient, in a non-protected form, for example, can further improve the organoleptic properties by further reducing a potential source of grit. A wicking agent may also be used, although, such agents would generally not qualify as rapidly dissolvable under the circumstance. However, if used at all, the amount of wicking agent used in accordance with the present invention is controlled to minimize its impact. Rapidly water soluble means that the material will be dissolved within about 45 seconds of being wetted with saliva and/or the material must be at least "soluble" pursuant to U.S.P. XXIII, page 10, (1995).

Note that in the context of the present invention, dissolution relates to water soluble ingredients only. A coated active ingredient is often not water soluble at all and thus the tablet never completely dissolves. However, because of the high content of rapidly water soluble ingredients in accordance with the present invention most of that which is water soluble generally dissolves within the disintegration time of the tablet. Thus, for the same loading of a coated active ingredient, relatively less grit will be present at the time that the tablet has disintegrated.

The active ingredient can include pharmaceutical ingredients, vitamins, minerals and dietary supplements. Pharmaceutical ingredients may include, without limitation, antacids, analgesics, anti-inflammatories, antipyretics, antibiotics, antimicrobials, laxatives, anorexics, antihistamines, antianthelmatics, antidiuretics, antiflatulents, antimigraine agents, biologicals, antispasmodics, sedatives, antihypertensives, antihyperactives, tranquilizers, decongestants, beta blockers and combinations thereof. Also encompassed by the terms "active ingredient(s)," "pharmaceutical ingredient(s)" and "active agents" are the drugs and pharmaceutically active ingredients described in Mantelle, U.S. Pat. No. 5,234,957, in columns 18 through 21. That text of Mantelle is hereby incorporated by reference.

As used in this disclosure, the term "vitamin" refers to trace organic substances that are required in the diet. For the purposes of the present invention, the term "vitamin(s)" includes, without limitation, thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid, vitamin B₁₂, lipoic acid, ascorbic acid, vitamin A, vitamin D, vitamin E and vitamin K. Also included within the term "vitamin" are the coenzymes thereof. Coenzymes are specific chemical forms of vitamins. Coenzymes include thiamine pyrophosphates (TPP), flavin mononucleotide (FMM), flavin adenine dinucleotide (FAD), Nicotinamide adenine dinucleotide (NAD), Nicotinamide adenine dinucleotide phosphate (NADP), Coenzyme A (CoA), pyridoxal phosphate, biocytin, tetrahydrofolic acid, coenzyme B₁₂, lipoyllysine, 11-cis-retinal, and 1,25-dihydroxycholecalciferol. The term "vitamin(s)" also includes choline, carnitine, and alpha, beta, and gamma carotenes.

The term "mineral" refers to inorganic substances, metals, and the like required in the human diet. Thus, the term

"mineral" as used herein includes, without limitation, calcium, (calcium carbonate), iron, zinc, selenium, copper, iodine, magnesium, phosphorus, chromium and the like, and mixtures thereof. The term "dietary supplement" as used herein means a substance which has an appreciable nutritional effect when administered in small amounts. Dietary supplements include, without limitation, such ingredients as bee pollen, bran, wheat germ, kelp, cod liver oil, ginseng, and fish oils, amino-acids, proteins and mixtures thereof. As will be appreciated, dietary supplements may incorporate vitamins and minerals.

In general, the amount of active ingredient incorporated in each tablet or dosage form may be selected according to known principles of pharmacy. An effective amount of pharmaceutical ingredient is specifically contemplated. By the term "effective amount," it is understood that, with respect, to for example, pharmaceuticals, a "pharmaceutically effective amount" is contemplated. A "pharmaceutically effective amount" is the amount or quantity of a drug or pharmaceutically active substance which is sufficient to elicit the required or desired therapeutic response, or in other words, the amount which is sufficient to elicit an appreciable biological response when administered to a patient. As used with reference to a vitamin or mineral, the term "effective amount" means an amount at least about 10% of the United States Recommended Daily Allowance ("RDA") of that particular ingredient for a patient. For example, if an intended ingredient is vitamin C, then an effective amount of vitamin C would include an amount of vitamin C sufficient to provide 10% or more of the RDA. Typically, where the tablet includes a mineral or vitamin, it will incorporate higher amounts, preferably about 100% or more of the applicable RDA.

The amount of active ingredient used can vary greatly. Of course, the size of the dosage form, the requirements of other ingredients, and the number of, for example, tablets which constitute a single dose will all impact the upper limit on the amount of pharmacologically active ingredient which can be used. However, generally, the active ingredient is provided in an amount of between greater than zero and about 80% by weight of the finished tablet and, more preferably, in a range of between greater than zero and about 60% by weight thereof. Put in other terms, the active ingredient can be included in an amount of between about 1 microgram to about 2 grams, and more preferably between about 0.01 and about 1000 milligrams per dosage form, i.e., per tablet.

The active ingredient can be provided directly, particularly when it does not have a particularly objectionable taste, i.e., a taste which can not be masked by traditional measures such as the use of sweeteners, flavors and the like. In fact, there may be particular advantages to using bulk active ingredients in this fashion when the active ingredient is rapidly water soluble. As discussed herein, the higher the level of rapidly water soluble ingredients, the greater the improvement in the rate of dissolution and the organoleptic feel of the dosage form in the mouth of the patient.

However, the active ingredient is preferably in a particle, granular, microgranular or crystalline form protected by a protective material. This protective material can be an adsorbate, a microgranule such as disclosed in Sparks et al., U.S. Pat. No. 4,940,588, or a coating which forms microcapsules and/or microparticles as described in, without limitation, Wehling et al., U.S. Pat. No. 5,178,878. Combinations of these are also contemplated, i.e., a coated adsorbate. In addition, protection can be provided by agglomeration or the formation of a matrix as is conventional. The dosage forms of the present invention may also include a

plurality of different active agents each protected by a different means.

The protective materials used in accordance with the present invention may include any of the polymers conventionally utilized in the formation of microparticles, matrix-type microparticles and microcapsules. Among these are cellulosic materials such as naturally occurring cellulose and synthetic cellulose derivatives; acrylic polymers and vinyl polymers. Other simple polymers include proteinaceous materials such as gelatin, polypeptides and natural and synthetic shellacs and waxes. Protective polymers may also include ethylcellulose, methylcellulose, carboxymethyl cellulose and acrylic resin material sold under the registered trademark EUDRAGIT by Rhone Pharma GmbH of Weiterstadt, Germany.

Generally, when a coating is used, it is preferred that the coating be used in at least about 5 percent based on the weight of the resulting particles. More preferably, the coating should constitute at least about 10 percent by weight of the particle. The upper limit of protective coating material used is generally less critical, except that where a rapid release of the active ingredient is desired, the amount of coating material should not be so great that the coating material impedes the release profile of the active agent or pharmaceutical ingredient when ingested. Thus, it may be possible to use greater than 100 percent of the weight of the core, thereby providing a relatively thick coating. Generally, however, no more than about 96 percent of the weight of the particle (drug and coating) will be coating material and, more preferably, no more than about 75 percent of the weight of the particulate will be coating. Described another way, the protective material is generally provided in an amount of between about 5 and about 96% by weight of the protected particle. More preferably, the amount is provided in a range of between about 5 and about 75% by weight based on the weight of the active protected ingredient. Of course, the use of coatings to provide for a sustained or controlled release may change these requirements. See Barry et al., U.S. Pat. No. 5,055,306, the text of which is hereby incorporated by reference and a copy is attached.

Particles formed from the active ingredients in accordance with the present invention may range in size from a few microns to as much as 1,500 microns. The lower limit of the size is not important, provided integrity is not compromised. Particles should generally not be larger than 1,200 microns and preferably be no larger than 850 microns. Of course, the larger the particles, the greater the impact on the organoleptic feel of the formulation once the dosage form dissolves.

Particles in accordance with the present invention generally relate to discrete particles containing an active ingredient and a coating protective material, if any. Particles may be a discrete granular material which has been independently and substantially (greater than about 90% of the particles completely coated) coated with a coating material.

Of course, when coated particles are produced, it is preferred that each individual unit of active ingredient, whether in the form of a liquid, a granule, or a powder, be substantially completely coated. In the case of, for example, extended release or sustained release microparticles, (also referred to as controlled release, delayed release or modified release), providing such complete coating helps ensure the desired level and type of release. When using an encapsulant or a coating to assist in taste-masking, complete coating helps ensure that the tastebuds of a patient are not exposed to the objectionable-tasting material. The more successful

and complete the coating the better, in terms of its intended properties. When, for example, rapid-release enteric coatings are used, substantially complete coating or encapsulation helps ensure that the active ingredient is not exposed to moisture or acid in the stomach. Thereafter, once the encapsulated drug reaches the intestines, the coating can, for example, disintegrate or rapidly dissolve such that it provides minimal interference with the normal dissolution profile of the drug when compared to the uncoated drug. In this aspect of the present invention, however, the term particle also includes a crystalline or granular base material which has been imperfectly coated such that some or all of the particles are not completely coated with the protective material. Also useful in accordance with the present invention and falling within the scope of the term particle, are agglomerate matrices whereby an agglomerate is dispersed in a wet coating material which is later broken up, ground or milled. The result may be incompletely coated particles or particles which are stuck together with the coating material serving as the glue.

For example, under certain circumstances, the use of an agglomerate matrix will provide adequate taste-masking and/or adequate protection of the active ingredient. Alternatively, the use of a matrix and/or agglomerates may sufficiently slow the rate of release of the active ingredient so as to allow it to be a sustained release formulation. In addition to the coating materials just described, various other additives, such as, for example, cross linkers, pore-formers, swelling agents, solubility modifiers, glidants, plasticizers and the like, may be included within the coating or protective material.

Ingredients and methods for making particles, including microcapsules, coated granules, agglomerates, etc., are well-known in the art and all such methods are contemplated. Methods of microencapsulation, for example, are described in the aforementioned Lieberman text, *Pharmaceutical Dosage Form. Tablets Volume 1*, Second Edition, New York, 1989, at pages 372-376. The disclosure of Lieberman is hereby incorporated by reference herein. One method taught in Lieberman is the technique of phase separation or coacervation which involves processing three mutually immiscible phases, one containing the pharmaceutical ingredient, another containing the protective coating material and a third containing a liquid vehicle used only in the manufacturing phase. The three phases are mixed and the protective material phase deposits by absorption on the pharmaceutical ingredient phase. After this step, the protective material phase is converted to a substantially solid form by cross-linking or by removal of solvent from this phase.

Other common techniques may be used for forming matrix-type particles wherein the pharmaceutical ingredient is dispersed in the protective material. For example, the pharmaceutical ingredient and a solution of a polymeric protective material may be sprayed to form droplets and contacted with a gas such as hot air so as to remove the solvent from the droplets. Such a mixture may also be dried to a solid and then comminuted to form the particles. Alternatively, the mixture of the pharmaceutical ingredient and polymeric solution may be mixed with an immiscible liquid phase and the solvent may be removed through this phase. The mixing step may include emulsification of the phase bearing the pharmaceutical ingredient and the protective material in the immiscible liquid phase. Preferably, a spray coating or coacervation coating technically may be used.

Sustained release in accordance with the present invention means that the active ingredient is released into the blood-

stream in a manner which is intentionally slower than the bioavailability of the same drug if administered in a non-sustained released form such as in bulk. Generally, a drug will exhibit at least a 25% decrease in its rate of absorption bioavailability relative to the uncoated drug. Most preferably, sustained release formulations are formulations which administer the active ingredient over a period of ten hours or greater and most preferably, between about 12 and about 24 hours. All such release rate control in the formulations of the present invention must come from the particles themselves as, ideally, the remainder of the dosage form has dissolved.

In contrast, rapid release dosage forms in accordance with the present invention are those in which the drug is rapidly released from the encapsulant, coating, or other protective material when desired. To the extent possible, the effect of the protective material under such circumstances will be minimal in terms of reducing the normal bioavailability of the same drug if unprotected. Thus, for example, where a coating is used to taste mask the objectionable flavor of a material, it is important that that coating be intact, to the extent necessary to serve its taste-masking function, while the dosage form is in the mouth of the patient. However, once the patient has swallowed there is no longer a need to protect the taste buds from the drug. It may be desirable that the drug be immediately bioavailable. In such a circumstance, it is desirable for the coating to either rupture in order to release its contents, dissolve thereby exposing its contents or allow the gastric juices in the stomach to permeate through and dissolve the active ingredient such that the bioavailability of the coated drug remains, as nearly as possible, the same as that of the same drug if administered in an unprotected form. Thus, if a tablet including non-protected active ingredients would need normally to be dosed every four or every six hours, then the rapid release dosage form in accordance with the present invention would also have to be administered on that same basis. A rapid release dosage form in accordance with the present invention is one which disintegrates rapidly in the mouth to form a suspension of particles which, once they clear the mouth, will release their contents so as not to interfere with the normal bioavailability of the active ingredient.

Generally, the particles in accordance with the present invention are provided in an amount of between greater than zero to about 75% by weight based on the weight of the finished dosage form. More preferably, the particles are provided in an amount of between greater than zero and about 60% by weight.

In attempting to balance the various competing objectives of the dosage forms of the present invention, namely; compressibility at conventional pressures, hardness and friability (which allow for certain processing and packaging advantages) and rapid dissolution in the mouth, several traditionally held values within the pharmaceutical industry had to be transgressed. This is most apparent from the composition of the matrix and its effects on these dosage forms. The matrix includes at least two ingredients: a non-direct compression filler and a lubricant. The use of both ingredients, particularly in the amounts contemplated, really sets the present invention apart. The matrix will assist in preventing the rupture of any microcapsules, microparticles or other protected active ingredient incorporated therein during compression. The matrix will also assist in the rapid dissolution of the dosage form in the mouth. Finally, the matrix provides a positive organoleptic experience to the patient.

The type of filler used provides one example of the uniqueness of the matrix and the dosage forms of the

invention. As illustrated by Cousins et al., it is traditional to use a direct compression sugar or other highly compressible fillers when attempting to produce tablets of a certain hardness and/or friability. However, it was determined that the particle sizes of such sugars had a dramatic effect on the manner in which the resulting tablets behave and feel in the mouth. While such sugars will eventually dissolve, because of their particle size and the processing that was done to improve their compressibility and fluidity, significant time is necessary before dissolution is complete. Thus, while the use of such sugars may allow for the tablet to disintegrate within the mouth, the result is relatively slow and a relatively high proportion of grit is generated. (Grit in the Cousins et al. formulation are attributable to the coated active ingredient, the relatively high proportion of non-water soluble excipients such as disintegrants, as well as the relatively large grained direct compression sugars used.)

Of course, one might expect to be able to overcome this particular problem by changing the particle size of the direct compression sugar, such that it will dissolve more quickly. However, as is well known in the pharmaceutical industry, decreasing the particle size of the sugar decreases its compressibility and fluidity. This was thought to undermine the ability to produce uniformly hard, and non-friable tablets. While such smaller particles might dissolve rapidly within the mouth, they were thought to be difficult, if not impossible, to compress, particularly at production speeds; thus, the need for specialized direct compression versions of these same sugars.

Therefore, it was surprising to discover that non-direct compression fillers may in fact be used in the production of a hard, non-friable, directly compressible, yet rapidly dissolvable, in-mouth dosage form, particularly in an automated, commercial production setting.

Any conventional material can be used as a filler in accordance with the present invention, so long as it meets the overall objectives hereof. The filler must be rapidly dissolvable when a tablet produced from same is placed in the mouth. This means that the material must be significantly rapidly water soluble. In addition, generally, the particle size of the filler will be relatively small, particularly compared to direct compression fillers.

Generally, direct compression excipients, particularly fillers and binders, are specialty excipients. In most cases, they are common materials that have been physically modified to impart greater fluidity and compressibility. In the case of sugars, such as, for example, dextrose, this generally means granulation to increase particle size. Direct compression mannitol, for example, generally has a minimum of at least about 80% average particle size over 100 microns. Other commercially available direct compression mannitols have a minimum particle size standard of greater than 90% over 200 microns. The opposite is true of the fillers in accordance with the present invention. While direct compression fillers may have at least 85% of the particles over 100 microns in size, often 85% of the particles of filler used in the present invention are significantly under 100 microns. In accordance with the present invention, average particle size generally ranges from between about 10 and about 80 microns, and most preferably, between about 20 to about 65 microns.

Particularly preferred fillers, in accordance with the present invention are non-direct compression sugars and sugar alcohols which meet the specifications discussed above. Such sugars and sugar alcohols include, without limitation, dextrose, mannitol, sorbitol, lactose and sucrose. Of course, dextrose, for example, can exist as either a direct

compression sugar, i.e., a sugar which has been modified to increase its compressibility, or a non-direct compression sugar.

Generally, the balance of the formulation can be matrix. Thus the percentage of filler can approach 100%. However, generally, the amount of non-direct compression filler useful in accordance with the present invention ranges from about 25 to about 95%, preferably between about 50 and about 95% and more preferably from about 60 to about 95%. In contrast, the prior art, as represented by Cousins et al. uses only up to about 42% of a filler and it is a direct compression sugar as well.

It has also been surprisingly found that when formulating dosage forms in accordance with the present invention, a relatively high proportion of lubricant should be used when compared to the prior art. Lubricants, and in particular, hydrophobic lubricants such as magnesium stearate, are generally used in an amount of between about 0.25 to about 5%, according to the Handbook of Pharmaceutical Excipients. However, as Cousins et al. amply demonstrate, when making a rapidly disintegrable tablet for direct in-mouth administration, one would seek to minimize the amount of magnesium stearate or other lubricant used. These hydrophobic lubricants generally interfere with disintegration and dissolution. They can also interfere with the compressibility of the material hindering the ability to make hard, non-friable tablets and the like. Not surprisingly, Cousins et al., who were seeking to make hard tablets that will rapidly disintegrate, teach the use of an amount of magnesium stearate which ranges from between about 0.4 to about 0.5% by weight, i.e., at the lower portion of the conventional range.

Moreover, the generally high level of non-direct compressible filler and the relatively low proportions of disintegrants used (if at all) in accordance with the present invention, would also lead one to expect to minimize the amount of lubricant used. However, it has been found that the amount of lubricant used can be double, triple or even quadruple that proposed in Cousins et al. Specifically, the amount of lubricant used can generally range from between about 1 to about 2.5% by weight, and more preferably between about 1.5 to about 2% by weight. Yet, despite the use of this relatively high rate of lubricant, the formulations in accordance with the present invention still exhibit a superior compressibility, hardness, and rapid dissolution within the mouth.

Hydrophobic lubricants useful in accordance with the present invention include alkaline stearates, stearic acid, mineral and vegetable oils, glyceryl behenate and sodium stearyl fumarate. Hydrophilic lubricants can also be used.

The dosage forms in accordance with the present invention preferably have a hardness of at least about 15 Newtons and are designed to dissolve spontaneously and rapidly in the mouth of a patient in less than about 90 seconds to thereby liberate the particles. Preferably the dosage form will dissolve in less than 60 seconds and even more preferably 45 seconds. This measure of hardness is based on the use of small tablets of less than about 0.25 inches in diameter. A hardness of at least about 20 Newtons is preferred for larger tablets. Most preferably, however, the dosage forms in accordance with the present invention have a hardness of between about 20 and about 50 Newtons and, more preferably, between about 25 and about 45 Newtons. Most preferably, the tablet will have a hardness of about 35 Newtons. Proportionate hardnesses are expected for tablets of different sizes.

It is quite surprising, however, that while relatively hard tablets can be produced in accordance with the present invention (hardnesses of 15–20 Newtons through about 50 Newtons) and despite the absence of traditionally directly-compressible fillers, relatively modest compressive force is required to produce substantially hard tablets in accordance with the present invention. Cousins et al. teach compaction forces of between 16 and 21 kN. Moreover, the minimum compressive force required for pure tablets of granular mannitol, i.e., a direct compression sugar, is at least 7.35 kN. However, in accordance with the present invention, rapidly dissolving tablets can be produced using compaction forces ranging from between about 3 to about 13 kN. This has significant advantages in terms of maintaining the structural integrity of any protective layer which may coat the active ingredient. In addition, it reduces the stress and wear on tablet-press equipment.

Unexpectedly, the dosage forms in accordance with the present invention will have a friability, as measured by U.S. Pharmacopoeia 23, 1995, Chap. 1216 entitled "Tablet Friability," of less than about 2% and, more preferably, less than about 1%. Thus, it is possible in accordance with the present invention to produce in-mouth, rapidly disintegrable dosage forms, including those having effervescent couples, which have friabilities comparable to those of conventional tablets. This allows the dosage forms of the present invention to be produced using traditional high-speed tablet presses. In addition, the resulting tablets can be stored in bulk and transported to packaging devices using traditional high-speed conveyors and/or, for example, vibrational conveyors.

Another aspect of the present invention is a method of making a packaged, orally disintegrable tablet or other dosage form. The method includes the steps of forming a mixture of the active ingredient and the matrix; and compressing the mixture to form a plurality of hard, compressed, rapidly disintegrable tablets adapted for direct oral dosing. Preferably, tablets are formed by "direct compression." "Direct compression" as used herein means that one can avoid the difficulty and expense of a wet or dry granulation prior to compression. The tablets will preferably have a hardness of at least about 15 Newtons and will be adapted to dissolve in the mouth of a patient within about 90 seconds to liberate the particles. In most formulations, the hardness may be at least 20 Newtons and the tablet dissolves in 45 seconds or less. Other conventional tableting or slugging methods known in the art are also contemplated. Indeed, any method in which a mixture of the active ingredient, often in the form of a protected particle, and the matrix are compressed into a solid dosage form having the properties disclosed herein are acceptable. After tableting or slugging, the dosage forms can be packaged in the lumen of a package or stored in bulk.

One of the principle advantages of the orally dissolvable tablets of the present invention is that they can be manufactured and stored in drums, bulk bins or hoppers, after tablet compression as is typical for tablets in the pharmaceutical industry. This is a property which is not found in most rapidly orally disintegrable tablets because of their friability. In turn, this attribute provides several significant advantages. First, with most friable, orally disintegrable tablets, the rate limiting step in production is the speed at which the tablets can be individually handled and placed in a protective, usually specially designed, blister-style package. The tablets are too fragile to withstand the forces involved in being dumped into the bulk-hopper of a packager or into some other form of intermediate or long-term

storage vessel. Thus, the speed of production of the tablets is limited by the rate of packaging.

In accordance with the present invention, however, because of the relatively low friability and the hardness of the resulting orally dissolvable tablets, they can be dumped into a hopper in bulk or can be stored in drums or other containers. This allows the manufacturer to complete production of the tablets at maximum tableting speed. Tablet presses can then be dedicated to other products while the orally disintegrable tablets of the present invention are packaged as is convenient.

Storing in bulk, in accordance with the invention, does not mean that tablets need to be stored for a long time. The residence time of tablets as they are dumped, in bulk, into the feed hopper of a high speed packager is contemplated.

The present invention allows for quality control of the tablets before they are packaged. This is of tremendous significance to the cost of production. Standard quality control procedures on orally disintegrable tablets involves testing the tablets that result from the line, i.e., tablets that have already been packaged. If a batch or lot of tablets has to be failed, the materials and the packaging may be lost. In some instances, the cost of the packaging is significantly higher than the cost of the drug material itself. By unshackling the tablet production and tablet packaging operations, one can test the tablets before package and therefore, eliminate the added expense of throwing away perfectly good packaging.

In addition, because of the relatively low friability and hardness of the orally dissolvable tablets in accordance with the present invention, it is possible to provide tablets in less costly and more cost-effective packaging. Currently, fragile, orally disintegrable dosage forms must be individually packaged in a very protective and very expensive blister pack. However, the tablets of the present invention can be placed in conventional openable and reclosable multi-tablet bottles or other similar packaging. That is to say that in accordance with the present invention, it is possible to provide more than a single dose in the lumen of a single, reopenable and reclosable package. Not only are such packages considerably less expensive over the cost of the number of tablets provided, but they are also far more efficient in terms of processing. In addition, two-sided foil and other relatively soft, pliant envelope-type packages may be used in combination with the tablets in accordance with the present invention. It is not possible to use such packages, or even less protective blister-packs, with the relatively friable orally-disintegrable tablets of the prior art.

In addition, in accordance with the present invention, conventional tablets feeders can be used to feed the tablets into any type of packaging equipment. Not only can the friable tablets of the prior art not withstand traditional hopping or storage, they also cannot withstand the forces involved in traditional feeding systems. Such systems normally consist of mechanisms which take bulk random tablets, capture them, align them, and place them into a package.

This provides a tremendous advantage in terms of the processability of tablets of the present invention and also provides tremendous advantages in terms of capital expenditures. By the use of the present invention, one can produce tablets which can be processed through totally conventional tableting methodologies and using conventional tableting equipment. This saves thousands to hundreds of thousands of dollars by removing the need for specialized packaging and handling equipment. It also increases the through-put of the tablets in question.

Another surprising aspect of the present invention is its workability. Cousins et al. uses a direct compression sugar and takes a mixture of all of its excipients and prepares them by dry or wet granulation prior to mixing with the active ingredient. This is a conventional method of improving the compressibility of materials and is often used even when direct compression excipients are employed.

However, the formulations of the present invention, despite their use of relatively high amounts of generally non-directly compressible fillers, can be formulated using direct compression. Direct compression involves mixing the various ingredients in a mixing vessel and then metering them directly into a tablet press whereupon they are pressed into tablets.

It is also surprising that, in accordance with the present invention, rapidly dissolving tablets can be manufactured with not only high levels of lubricant, but also that lubricant blend times of 10 to 25 minutes and greater can be used. However, according to the present invention, blend times of ten minutes and greater can be used without compromising compressibility, disintegration and dissolution of the tablets. In fact, this even improves the flow characteristics of this material.

In summary, it has been found that non-direct compression fillers, namely powdered mannitol, can be directly compressed, using lower than expected compression forces, at fairly high levels of lubricant and long lubricant blending. The result is a hard, yet rapidly orally dissolvable tablet.

In accordance with the present invention, the dosage forms can have any size conventional in the industry. However, dosage forms of up to about 2.54 centimeters or 1 inch, are generally preferable. It is also preferred that tablets produced have generally convex surfaces. Applicants have found that, by insuring that the tablet in question has as few sharp edges as possible, it is also possible to help retard the dusting or break-up of the tablets in accordance with the present invention, particularly during handling and shipping. Other shapes which retard the formation of sharp edges are also specifically contemplated hereby.

In addition to the ingredients previously discussed, the matrix may also include wicking agents, non-effervescent disintegrants and effervescent disintegrants. Wicking agents are compositions which are capable of drawing water up into the dosage form. They help transport moisture into the interior of the dosage form. In that way the dosage form can dissolve from the inside, as well as from the outside.

Any chemical which can function to transport moisture as discussed above can be considered a wicking agent. Wicking agents include a number of traditional non-effervescent disintegration agents. These include, for example, microcrystalline cellulose (AVICEL PH 200, AVICEL PH 101), Ac-Di-Sol (Croscarmellose Sodium) and PVP-XL (a crosslinked polyvinylpyrrolidone); starches and modified starches, polymers, and gum such as arabic and xanthan. Hydroxyalkyl cellulose such as hydroxymethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose, as well as compounds such as carbopol may be used as well.

The conventional range of non-effervescent disintegrant agents used in conventional tablets can be as high as 20%. However, generally, the amount of disintegration agent used ranges from between about 2 and about 5%, according to the Handbook of Pharmaceutical Excipients. Understandably, however, when a rapidly disintegrating dosage form is envisioned, the relative proportion of disintegration agent used will be increased. Cousins et al., for example, requires

from about 6.1 to about 13.3% reticulated PVP, as described in its various examples.

In accordance with the preferred embodiments of the present invention, the amount of wicking agents used ranges from between 2 to about 12% and preferably from between 2 to about 5%. This is surprising as tablets containing the same amount of the same materials used as disintegration agents normally exhibit disintegration times on the order of tens of minutes. In accordance with the preferred embodiments of the present invention, dissolution occurs in under 90 seconds and most preferably under 45 seconds. This also underscores the fact that while there may be some incidental disintegration due to the inclusion of these elements, their principle effect in the formulations of the present invention is that of a wicking agent.

It is also possible, of course, to include non-effervescent disintegrants which may not act to wick moisture, if desirable. In either event, it is preferable to use either rapidly water soluble, non-effervescent disintegrants or wicking agents and/or to minimize the use of generally non-water soluble wicking agents or non-effervescent disintegrants. Non-rapidly dissolvable, non-rapidly water soluble elements if used in sufficient quantity, can adversely affect the organoleptic properties of the tablets as they dissolve within the mouth and therefore should be minimized. Of course, wicking agents or non-effervescent disintegrants which are rapidly water soluble as discussed herein can be used in greater quantity and they will not add to the grittiness of the formulation during dissolution. Preferred wicking agents in accordance with the present invention include crosslinked PVP, although, the amounts of these must be controlled as they are not rapidly water soluble.

In addition, it may be desirable to use an effervescent couple, in combination with the other recited ingredients to improve the disintegration profile, the organoleptic properties of the material and the like. Preferably, the effervescent couple is provided in an amount of between about 0.5 and about 50%, and more preferably, between about 3 and about 15% by weight, based on the weight of the finished tablet. It is particularly preferred that sufficient effervescent material be provided such that the evolved gas is less than about 30 cm, upon exposure to an aqueous environment.

The term "effervescent couple" includes compounds which evolve gas. The preferred effervescent couple evolve gas by means of a chemical reaction which takes place upon exposure of the effervescent disintegration couple to water and/or to saliva in the mouth. This reaction is most often the result of the reaction of a soluble acid source and an alkali monohydrogencarbonate or other carbonate source. The reaction of these two general compounds produces carbon dioxide gas upon contact with water or saliva. Such water-activated materials must be kept in a generally anhydrous state and with little or no absorbed moisture or in a stable hydrated form, since exposure to water will prematurely disintegrate the tablet. The acid sources may be any which are safe for human consumption and may generally include food acids, acid and hydric antacids such as, for example: citric, tartaric, malic, fumaric, adipic, and succinic. Carbonate sources include dry solid carbonate and bicarbonate salt such as, preferably, sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and the like. Reactants which evolve oxygen or other gases and which are safe for human consumption are also included.

In the case of the orally dissolvable tablets in accordance with the present invention, it is preferred that both the

76
171

amount and the type of disintegration agent, either effervescent or non-effervescent, or the combination thereof be provided sufficient in a controlled amount such that the tablet provides a pleasant organoleptic sensation in the mouth of the patient. In some instances, the patient should be able to perceive a distinct sensation of fizzing or bubbling as the tablet disintegrates in the mouth. In general, the total amount of wicking agents, non-effervescent disintegrants and effervescent disintegrants should range from 0-50%. However, it should be emphasized that the formulations of the present invention will dissolve rapidly and therefore, the need for disintegrating agents is minimal. As illustrated in the examples, appropriate hardness, friability and dissolution times can be obtained even without effervescent disintegrants or high quantities of wicking agents.

The use of a non-direct compression filler eliminates the need for many conventional processing steps such as granulation and/or the need to purchase more expensive pregranulated, compressible fillers. At the same time, the resulting dosage form is a balance of performance and stability. It is robust enough to be conventionally produced using direct compression. It is robust enough to be stored or packaged in bulk. Yet, it rapidly dissolves in the mouth while minimizing the unpleasant feel of conventional disintegrating tablets to the extent possible.

This last point bears further emphasis, by the use of non-direct compression fillers, by maximizing the quantity of rapidly dissolving, rapidly water soluble ingredients and by the use of a relatively high lubricant content, dosage forms can be produced which can dissolve rapidly yet are robust as described herein. The difference between dissolution and disintegration is not a trivial one. Conventional disintegrating tablets may disintegrate in 45 seconds or less. However, because of the relatively high content of non-water soluble and non-rapidly water soluble components, what remains is material which cannot dissolve or has not dissolved. In contrast, and in accordance with the present invention, all of the rapidly water soluble materials have dissolved leaving a relatively small percentage of non-dissolved and/or disolvable material.

The following patents are hereby incorporated by: Cousins et al., U.S. Pat. No. 5,464,632; Chevkin, U.S. Pat. No. 4,613,497; Howell, U.S. Pat. No. 3,962,417; Cnoper, GB 3,160; Sparks et al., U.S. Pat. No. 4,940,588; Wehling et al., U.S. Pat. No. 5,178,878; Bolt et al., U.S. Pat. No. 5,225,197; and Barry et al., U.S. Pat. No. 5,055,306. These patents describe various active ingredients, excipients and general methods of making particles and dosage forms and they are included for that reason.

EXAMPLES

Example 1

80 mg APAP (acetaminophen), using Nu-Tab Compressible Sugar (sucrose) as filler:

Formula:	Coated APAP (20% coating)	15.4%
	Compressible Sugar	64.3%
	Effervescent	4%
	Sweetener	4.6%
	Glidant	0.3%
	Lubricant	1.5%
	Wicking Agent	5%

-continued

Flavor	3.8%
Color	0.3%
Total	650 mg total tablet weight

Tablets were produced using a direct compression method as follows: All of the material, except the lubricant were weighed and blended for a period of between about 30 and about 50 minutes. Thereafter, the lubricant was added and the mixture was blended for an additional 5 to 15 minutes. The blend was then tableted on a conventional 6 or 16 stage rotating tablet press at 25-30 revolutions per minute. Tablets were compressed using an average compression force of 10.36 kN—the average ejection force was 184.6 N. The average in-vitro disintegration time was 727.8 seconds and friability was 0.87%. The result was a slowly disintegrating tablet and an unpleasant, gritty organoleptic experience for the patients.

The following procedure was followed to determine in-vitro disintegration of tablets. A constant temperature water bath was turned on and allowed to equilibrate to 37° C. 150 mL of DI water was placed in 8oz. clear plastic cups, which in turn were placed in the constant temperature water bath. The water in the cups was allowed to equilibrate to 37° C., checking with a thermometer. Then, one tablet was placed in a cup and a stopwatch was started simultaneously. Disintegration was complete when the tablet had broken apart and only water insoluble or non-rapidly water soluble particles remained. When the tablet had reached the endpoint, the timer was stopped. Average and % RSD were calculated. In-vivo disintegration of Hard Tablets was measured as follows: Tablets were placed in the mouth and are sucked or moved around with the tongue. (Tablets are not chewed.) The tablet disintegration endpoint occurs when the body of the tablet has disintegrated into particles. The degree of dissolution at that point involved a consideration of the organoleptic properties of the amount of remaining particles.

Example 2

80 mg APAP using FINLAC DC (direct compression Lactitol) as filler:

Formula:	Coated APAP	15.4%
	FINLAC DC	64.3%
	Effervescent	4%
	Sweetener	4.6%
	Glidant	0.3%
	Lubricant	1.5%
	Wicking Agent	5%
	Flavor	3.8%
	Color	0.3%
	Total	650 mg total tablet weight

These tablets were produced as described in Example 1 and were compressed using an average compression force of 7.68 kN—the average ejection force was 162.1 N. The average in-vitro disintegration time was 100.2 seconds and friability was 0.99%. The result was a slowly disintegrating tablet and an unpleasant, gritty organoleptic experience for the patients.

Example 3

80 mg APAP using Sorbitol Instant Pharma (direct compression sorbitol) as filler:

17

Formula:	Coated APAP	15.4%
	Sorbitol Instant Phospha	64.3%
	Effervescence	4%
	Sweetener	4.6%
	Glidant	0.3%
	Lubricant	1.5%
	Wicking Agent	5%
	Flavor	3.8%
	Color	0.3%
	Total	650 mg total tablet weight

These tablets were produced as described in Example 1 and were compressed using an average compression force of 5.65 kN—the average ejection force was 122.3 N. The average in-vitro disintegration time was 227.2 seconds and friability was 1.14%. The result was a slowly disintegrating tablet and an unpleasant, gritty organoleptic experience for the patients.

Example 4

Coated Pantoicamel Powder (78.3%)	15.7%
Powdered Mannitol (non-direct compression sugar), USP	64.0%
Sodium Bicarbonate, No. 1 USP	2.3%
Citric Acid, Anhydrous Fine Granular USP	1.7%
Artificial sweetener, Dried	4.6%
Wicking Agent	5.8%
Glidant	0.3%
Magnesium Stearate, NF	1.5%
Artificial Flavor	3.8%
Artificial Color	0.3%
	650.0 mg Total tablet weight

Two different batches of these tablets were produced. In the first batch, tablets were produced as described in Example 1. The resulting tablets had a hardness of 35 Newtons and a friability of 1.8%. The average in-vitro disintegration time was 36 seconds. The second batch was produced as described in Example 1. The average in-vitro disintegration time was 44 seconds and the tablets had a hardness of 50 Newtons and a friability of 0.5%. The result was a fast dissolving tablet with a minimum of grit and a pleasant organoleptic experience.

Example 5

Pseudoephedrine HCl/Chlorpheniramine Maleate; ½"

Formula:	Coated Pseudoephedrine HCL (40% coated)	5%
	Coated Chlorpheniramine Maleate (90% coated)	2%
	Powdered Mannitol	71.9%
	Effervescence	4%
	Sweetener	4.8%
	Glidant	0.3%
	Microcrystalline Cellulose	2%
	Lubricant	1.5%
	Wicking Agent	5.8%
	Flavor	2.4%
	Color	0.3%
	Total	500 mg total tablet weight

These tablets were produced as described in Example 1 and compressed with an average force of 9.38 kN (38 N hardness), and average ejection force of 212.2 N. The tablets

18

disintegrated in 22.83 seconds in vitro and 20–30 seconds in vivo. At that time, most, if not all of the rapidly water soluble ingredients (> about 75%) had dissolved. Friability was 1.37%.

Example 6

Cimetidine Tablets, ½"

Formula:	Coated Cimetidine (32% coated)	22.5%
	Powdered Mannitol	60.2%
	Effervescence	4%
	Sweetener	5%
	Wicking Agent	6%
	Glidant	0.3%
	Lubricant	1.5%
	Flavor	0.5%
	Total	650 mg total tablet weight

These tablets were produced as described in Example 1 and were compressed with an average force of 8.52 kN (43 N) hardness, and an average ejection force of 215.6 N. The tablets disintegrated in 26.31 seconds in vitro and 20–30 seconds in vivo. Friability was 1.12%.

Example 7

Acetaminophen, ½"

Formula:	Coated APAP (20% coating level)	31.3%
	Powdered Mannitol	49.6%
	Effervescence	4%
	Sweetener	5%
	Microcrystalline Cellulose	2%
	Glidant	0.3%
	Lubricant	1.5%
	Wicking Agent	5.8%
	Flavor	0.5%
	Total	1,000 mg total tablet weight

These tablets were produced as described in Example 1 and were compressed with an average force of 12.13 kN (approx. 83 N hardness), and had an average ejection force of 286.4 N. The tablets disintegrated in 23.42 seconds in vitro and 30–40 seconds in vivo. Friability was 0.82%.

Example 8

80 mg APAP, ½"

Formula:	Coated APAP (20% coated)	15.4%
	Powdered Mannitol	66.6%
	Citric Acid	1.7%
	Sweetener	4.6%
	Glidant	0.3%
	Lubricant	1.5%
	Wicking Agent	5.8%
	Flavor	3.8%
	Color	0.3%
	Total	650 mg total tablet weight

These tablets produced as described in Example 1 and were compressed with an average force of 10.27 kN (40 N hardness) and had an average ejection force of 223.87 N. The tablets disintegrated in 20.42 seconds in vitro and in

20-30 seconds in vivo. The friability was 1.0%. It should be noted that the above formulation, while having a hardness of 40 Newtons and a friability of 1%. Disintegration and indeed, dissolution occurred in between 20 and 30 seconds, without the use of an effervescent disintegrant.

Example 9

APAP coated with 10% Eudragit— $\frac{1}{2}$ " hard tablet—target hardness is 95 N+/-10 N.

Formula:	Coated Acetaminophen (10% coating factor)	944 mg
	Aspartame	50 mg
	Disintegrant	89 mg
	Lubricant	5 mg
	Flavor	12 mg
Total		1100 mg total tablet weight

Tablets were compressed using an average compression force of 23.28 kN (109 N Hardness) and had an average ejection force of 802.8 N. Disintegration time in vitro was 43.90 seconds in vivo was greater than 40 seconds. Friability was not measured. Tablets tasted terrible and were extremely gritty.

Example 10

Coated APAP (7% coated with ethylcellulose)	530 mg
Compressible Sugar	160 mg
Microcrystalline Cellulose	90 mg
Croscopollose	60 mg
Sodic Carboxymethylcellulose	50 mg
Silicon Dioxide	6 mg
Lubricant	4 mg
Sweetener	25 mg
Flavor	15 mg
Magnesium Trisilicate	50 mg
Total	990 mg total tablet weight

Tablets were compressed using an average compression force of 35.68 kN (101 N Hardness) and had an average ejection force of 362.8 N. Disintegration time in vitro was 65.59 seconds.

Examples 9 and 10 are very similar to the formulations described in the Cousins et al. patent discussed herein. These examples illustrate many of the advantages of the present invention. First, it should be noted that in both cases, the relative proportion of rapidly water soluble materials was minimal. Thus, when these tablets disintegrate, the patient is left with a mouth full of particulate materials which must be swallowed, rather than a slurry or solution as would result from the present invention. At very least, the present invention would minimize the level of particulate and grit. Second, while the formulations of examples 9 and 10 could disintegrate in about 45 and about 65 seconds respectively, the formulations of the present invention as illustrated in the examples 4-8 were able to dissolve in 40 seconds or less, often in about 20 seconds. Finally, the content of the matrix, both in terms of direct versus non-direct compression materials, as well as the percentage of disintegrants used in accordance with the Cousins et al. formulation, were considerably higher, adding to the unpleasant gritty feel of the disintegrated formulation. The invention minimizes this and, where possible, the only grittiness is a result of the coated active material and a relatively minor percentage of other excipients.

We claim:

1. A hard, compressed, rapidly dissolvable dosage form adapted for direct oral dosing comprising: an active ingredient and a matrix including a non-direct compression filler and a lubricant, said dosage form being adapted to rapidly dissolve in the mouth of a patient and thereby liberate said active ingredient, and having a friability of about 2% or less when tested according to the U.S.P., said dosage form having a hardness of at least about 15 Newtons.
2. The dosage form as claimed in claim 1 wherein said friability is less than or equal to about 1%.
3. An openable and recloseable package containing a plurality of hard, compressed, rapidly dissolving tablets adapted for direct oral dosing comprising: particles including an active ingredient and a protective material, said particles being provided in an amount of between about 0.01 and about 75% by weight based on the weight of said tablets; and a tablet matrix including a non-direct compression filler and a hydrophobic lubricant; said tablet matrix comprising at least about 60% rapidly water soluble ingredients based on the total weight of the matrix material; said tablet having a hardness of between about 15 and about 50 Newtons, a friability of less than 2% when measured by U.S.P. and being adapted to both dissolve spontaneously in the mouth of a patient in less than about 60 seconds and thereby liberate said particles.
4. The dosage form as claimed in claim 1 wherein said hardness ranges from between about 20 Newtons and about 50 Newtons.
5. The dosage form as claimed in claim 4 wherein said hardness is about 35 Newtons.
6. The dosage form as claimed in claim 1 wherein said dosage form will dissolve in about 90 seconds or less.
7. The dosage form as claimed in claim 6 wherein said dosage form will dissolve in about 60 seconds or less.
8. The dosage form as claimed in claim 7 wherein said dosage form will dissolve in about 45 seconds or less.
9. The dosage form as claimed in claim 1 further comprising at least one particle, said particle including said active ingredient and a protective material.
10. The dosage form as claimed in claim 9 wherein said protective material is selected from the group consisting of an adsorbate, microgranule, a matrix or a coating.
11. The dosage form as claimed in claim 10 wherein said protective material is a coating.
12. The dosage form as claimed in claim 11 wherein said coating constitutes at least about 5% of the particle by weight.
13. The dosage form as claimed in claim 11 wherein said coating constitutes between about 5% and about 75% of the particle by weight.
14. The dosage form as claimed in claim 1 wherein said non-direct compression filler is present in an amount of between about 25 and about 95% by weight.
15. The dosage form as claimed in claim 14 wherein said non-direct compression filler is present in an amount of between about 50 and about 95% by weight.
16. The dosage form as claimed in claim 15 wherein said non-direct compression filler is present in an amount of between about 60 and about 95% by weight.
17. The dosage form as claimed in claim 1 wherein said non-direct compression filler is a non-direct compression sugar or non-direct compression sugar alcohol.
18. The dosage form as claimed in claim 1 wherein said active ingredient is selected from the group consisting of systematically distributable pharmaceutical ingredients, vitamins, minerals and dietary supplements, as well as non-systematically distributable pharmaceutical ingredients.

21

19. The dosage form as claimed in claim 18 wherein said pharmaceutical ingredients include antacids, analgesics, anti-inflammatories, antipyretics antibiotics, antimicrobials, laxatives, anorexics, antihistamines, antiasthmatics, antidiuretics, antilipidemics, antimigraine agents, antispasmodics, sedatives, antihyperactives, antihypertensives, tranquilizers, decongestants, beta blockers and combinations thereof.

20. The dosage form as claimed in claim 1 wherein said active ingredient is provided in an amount between about greater than zero and about 80% by weight of the finished dosage form.

21. The dosage form as claimed in claim 20 wherein said active ingredient is provided in an amount between about greater than zero and about 60% by weight of the finished dosage form.

22. The dosage form as claimed in claim 9 wherein said particles are provided in an amount between about greater than zero and about 75% by weight of the finished dosage form.

23. The dosage form as claimed in claim 22 wherein said particles are provided in an amount between about greater than zero and about 60% by weight of the finished dosage form.

24. The dosage form as claimed in claim 9 wherein said particles are rapid release particles.

25. The dosage form as claimed in claim 9 wherein said particles are sustained release particles.

26. The dosage form as claimed in claim 1 wherein said lubricant is a hydrophobic lubricant.

27. The dosage form as claimed in claim 26 wherein said hydrophobic lubricant is provided in an amount of between about 1 and about 5% by weight.

28. The dosage form as claimed in claim 27 wherein said hydrophobic lubricant is provided in an amount of between about 1 and about 2.5% by weight.

29. The dosage form as claimed in claim 28 wherein said hydrophobic lubricant is provided in an amount of between about 1.5 and about 2% by weight.

30. The dosage form as claimed in claim 1 further comprising a wicking agent.

31. The dosage form as claimed in claim 30 wherein said wicking agent is provided in an amount of less than about 5% by weight.

32. A hard, compressed, rapidly dissolving tablet adapted for direct oral dosing comprising: particles including an active ingredient and a protective material, said particles being provided in an amount of between about 0.01 and about 75% by weight based on the weight of the tablet; and a matrix including a non-direct compression filler, a wicking

22

agent, and a hydrophobic lubricant; said tablet matrix comprising at least about 60% rapidly water soluble ingredients based on the total weight of the matrix material; said tablet having a hardness of between about 15 and about 50 Newtons, a friability of less than 2% when measured by U.S.P. and being adapted to dissolve spontaneously in the mouth of a patient in less than about 60 seconds and thereby liberate said particles and be capable of being stored in bulk.

33. The tablet of claim 32 wherein said non-direct compression filler has an average particle size of 90 microns or less, said filler being provided in an amount of between greater than about 25 and about 95% by weight of the tablet; said wicking agent being provided in an amount of between about 2 and about 5% by weight based on the weight of the tablet; and said lubricant being provided in an amount of between about 1.0 and about 2.5% by weight based on the weight of the tablet.

34. A tablet as claimed in claim 32 wherein said friability is less than or equal to about 1%.

35. A tablet as claimed in claim 32 wherein said hardness is about 35 Newtons.

36. A tablet as claimed in claim 32 wherein said tablet dissolves in less than about 45 seconds.

37. A method of making a packaged, orally disintegrable dosage form, comprising the steps of:

(a) forming a mixture including an active ingredient and a matrix including a non-direct compression filler and a lubricant;

(b) compressing said mixture to form a plurality of hard, compressed, rapidly disintegrable dosage forms having said active ingredient distributed in said orally dissolvable matrix, said dosage forms being adapted for direct oral dosing, said dosage forms having a hardness of at least about 15 Newtons and being adapted to dissolve spontaneously in the mouth of a patient in less than about 60 seconds and thereby liberate said active ingredient; and

(c) storing said tablets in bulk prior to packaging said tablets.

38. The method of claim 37 further comprising the step of packaging said tablets in a lumen of a package such that there is at least one tablet per package.

39. The method of claim 38 wherein a plurality of said compressed tablets are packaged in a single lumen of a single package.

40. The method of claim 37 wherein said compressing step is conducted using direct compression.

* * * * *

80
175

SUPERINDUSTRIA Y COMERCIO
Radiacion : 04002774 00000004 Folios: 89
Fecha (AMB): 2005-11-25 11:30:48
Tramite : 011 PCI-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 90,449
FECHA : NOVIEMBRE 25 DE 2005

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	030-00110-6	36876429	26/10/2005	1,175,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LEMAS COMERCIALES	235,000.00
		TOTAL :	235,000.00

BON: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____