145

Industria y Comercio
SUPERINTENDENCIA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05 124314 .00003.0000
Fec 2006-08-30 16:28:27 Dep 2000 DIRECCIONES
Tra 11 PATENTES II
Exe 379 EXENCIONALES
Act 400 OPUSIOBSERVTES Folios 50

FORMULARIO ÚNICO DE OPO

① OPOSICIÓN A :

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

② SOLICITUD PUBLICADA

Número del expediente: 05-124314
Solicitante: WARNER-LAMBERT COMPANY LLC.
Apoderado: PROCAPS S.A.
Título de la nueva creación o denominación del signo: "COMPOSICIONES FARMACEÚTICAS DE ATORVASTATINA".
Gaceta: 564

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 371 99 00 Fax: 373 08 18 E-mail:	**IDENTIFICACIÓN** C.C. [ ] NIT [X] C.E. [ ] Otro [ ] Cual Número 890.106.527-5
REPRESENTANTE O APODERADO	Nombre: REINALDO PINILLA MORENO Dirección: TRANSVERSAL 13 A #119-95 Teléfono: OFICINA 104 Fax: 2131213 6121979 E-mail: negocios@optimum-co.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número 80.425.609 TP 91563

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

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

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

⑥ **ANEXOS**

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

⑦

NOMBRE: REINALDO PINILLA MORENO

FIRMA: _____

C.C. 80425609 **TP.** 91563 CSJ

PRESENTACION PERSONAL

En Bogotá, D.C. a 29 AGO 2006 se presentó

en la Notaría Décima, cuyo titular es SERGIO FRANCO LEON

REINALDO PINILLA MORENO

Con cédula No. 80425609 TP. 91563.

Expedida en USAQUEN. y dijo _____ que

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

letra, En constancia se firma _____

REPUBLICA DE COLOMBIA
NOTARIO DECIMO
DE BOGOTA
SERGIO FRANCO LEON

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

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 05 124.314
Asunto	: Oposición a la solicitud de patente de Invención titulada "COMPOSICIONES FARMACÉUTICAS DE ATORVASTATINA".
Solicitante	: WARNER-LAMBERT COMPANY LLC..
Opositora	:PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 564 del 31 de Mayo de 2006

Yo, *REINALDO PINILLA MORENO*, abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad *PROCAPS S.A.* conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada *"COMPOSICIONES FARMACEUTICAS DE ATORVASTATINA"*, solicitada por *WARNER-LAMBERT COMPANY LLC.*, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Transversal 13ª Nº 119-95, Of. 104 Tel. (571) 2 13 12 13 – 6 20 50 21 – Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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 legitimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular Atorvastatina. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 7 de diciembre de 2005, reivindicando prioridad bajo la solicitud US60/477917 del 2003-06-12 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial Nº 564 del 31 de Mayo de 2006, página 370, Nº publicación 71, cuya publicación internacional corresponde a la WO2004/110406 del 23/12/2004.

2.2. La solicitud colombiana 05 124.314 objeto de la presente oposición, se refiere a una composición farmacéutica granulada en seco que comprende atorvastatina o una sal farmacéuticamente aceptable de la misma. La composición farmacéutica contiene menos de aproximadamente el 5% (p:p) de un aditivo de sal de metal

alcalinotérreo. La composición granulada en seco, después de almacenarla a 40°C y al 75% de humedad relativa durante 4 semanas, no contiene más de aproximadamente el 2% de impurezas totales y/o productos de degradación basándose en el área porcentual de los picos de HPLC relacionados con el fármaco. La composición se usa en la formación de una forma de dosificación unitaria sólida. La forma de dosificación unitaria se selecciona entre el grupo compuesto por un comprimido y una cápsula. La atorvastatina contiene al menos una forma de atorvastatina parcial o completamente desordenada o una sal farmacéuticamente aceptable de la misma. Igualmente reivindica un método de preparación, un método de tratamiento y un kit.

2.3. En primera instancia, se debe advertir que la reivindicación 14 se refiere al método terapéutico y según la legislación, decisión 486 de la Comunidad Andina de Naciones, 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: WO02072073, 2002-19-09.
- D2: US5686104, 1997-11-11.

2.5. Ahora bien, el documento D1, particularmente en el resumen y en la página 3, línea 24 a página 6 línea 16 y página 12 línea 17 a línea 29 y reivindicaciones, se refiere a una composición en forma de gránulos (reivindicación 19) que comprende atorvastatina cálcica como ingrediente activo (reivindicación 7) para el tratamiento de la hipercolesterolemia e hiperlipidemia. Según dicho documento anterior D1, se revela con anterioridad una preparación farmacéutica de atorvastatina cálcica que compreden una sustancia alcalina. Según dicho documento anterior, también se revela un proceso para la preparación de la formulación que comprende una o más componentes de relleno, de cubierta, sustancias alcalinas, sustancias básicas, surfactantes y otros ingredientes farmacéuticamente aceptables. Así las cosas, es claro que este documento D1, revela una misma propuesta como solución que incluye una composición en forma de gránulos (reivindicación 19) que comprende atorvastatina cálcica como ingrediente activo (reivindicación 7) para el tratamiento de la hipercolesterolemia e hiperlipidemia. Por lo tanto, a los ojos de este documento D1, la presente solicitud no es novedosa.

2.6. Ahora bien el documento D2, se refiere según su descripción y reivindicaciones, a un proceso donde la atorvastatina es combinada con un aditivo estabilizador tal como una sal de metal alcalinotérreo (reivindicación 7) así como excipientes para conformar una composición farmacéutica estable para el tratamiento de la hipercolesterolemia o hiperlipidemia. Según este documento D2, revela una forma ventajosa de bioestabilización de la atorvastatina. Así las cosas, si combinamos este documento D2 con lo referenciado en el documento anterior D1, la composición farmacéutica granulada en seco referenciada en el presente documento objeto de

oposición, seria obvia y se deriva evidentemente de lo expuesto en estos dos documentos anteriores. Por lo tanto a la luz de la combinación de los documentos D2 con lo expuesto en el documento D1, la solicitud carece de altura o nivel inventivo.

2.7. Ahora bien, del alcance de las reivindicaciones referida a un kit que contiene la composición farmacéutica, se refiere a que comprende una cantidad eficaz de atorvastatina o una sal farmacéuticamente aceptable en una forma de dosificación y un contenedor que incluye dicha forma de dosificación. Al respecto, se debe mencionar que dicho kit está integrado por un compuesto activo que hace parte del estado de la técnica. Por lo tanto carece de NOVEDAD el contenido del contendor del kit objeto de la solicitud. Por otro lado se debe advertir no existe *Unidad de Invención*, conforme el artículo 25, que reza: *"La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo"*. Como tal, es de reconocer que son objetos diferentes el contenido y el contenedor que lo recibe. Al margen de lo antes expuesto, un producto tal como un "kit", para ser patentable también debería cumplir con el requisito de *Unidad de Invención*; en este caso dicho kit es simplemente un contenedor que tienen un dosis que comprende un compuesto activo conocido, por lo tanto no constituye materia patentable. Por lo tanto, un kit de contendor estaría por fuera del objeto de la patente inicial que hace referencia es a un compuesto independiente del contenedor o receptáculo que lo contiene.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **05-124.314** 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:

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, 12 de junio de 2003, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, la composición farmacéutica granulada en seco sobre la 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, 12 de junio de 2003, a partir del documento D2 en combinación con D1, es posible deducir la conformación de la composición farmacéutica granulada en seco 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 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 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 todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presenté oposición y negar el registro Patente de invención denominada *"COMPOSICIONES FARMACEUTICAS DE ATORVASTATINA"*, solicitada por *WARNER-LAMBERT COMPANY LLC.*, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 564.

3. PRUEBAS

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

- D1: WO02072073, 2002-19-09.
- D2: US5686104, 1997-11-11.

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: WO02072073, 2002-19-09.
- D2: US5686104, 1997-11-11.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Transversal 13ª Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

REINALDO PINILLA MORENO
C.C. 80'425.609 de Bogotá
T.P.A. 91563 del C.S. de la J.

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

156

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-124314- -00003-0000
Fec: 2006-08-30 15:28:27 Dep: 2020 NUECREACIONES
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Ene: 379 FASENACIONALII
Act: 400 OPOSIOBSERVTER Folios: 60

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 66,262
FECHA : AGOSTO 29 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	48302514	27/07/2006	260,500.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99	OTROS SERVCIOS ADMINISTRATIVOS	75,500.00
			TOTAL : $	75,500.00

SON: SETENTA Y CINCO MIL QUINIENTOS PESOS

RESPONSABLE : _____

Gaceta. 157

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 24,195
FECHA : MARZO 27 DE 2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-124314- -00003-0000
Fec: 2006-03-30 15:26:27 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYR
Exs: 379 FASENACIONALII
Act: 400 OPOSIOBSERVTER Folios: 60

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	44744453	10/03/2006	260,500.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	9,500.00
		TOTAL : $	9,500.00

SON: NUEVE MIL QUINIENTOS PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

158

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 66,663
FECHA : AGOSTO 30 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	48302510	30/08/2006	390,500.00
OTECH LTDA.	CONSIGNACION	BANCO POPULAR	050-00110-6	48609469	30/08/2006	16,500.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	161,000.00
		TOTAL : $	161,000.00

SON: CIENTO SESENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

159

PROCAPS

PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **REINALDO PINILLA MORENO,** abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 91563 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **05124314**, de título: **"COMPOSICIONES FARMACÉUTICAS DE ATORVASTATINA"** de **WARNER - LAMBERT COMPANY,** publicada en la gaceta No. 564 del 31 de Mayo de 2006.

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

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

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

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto,

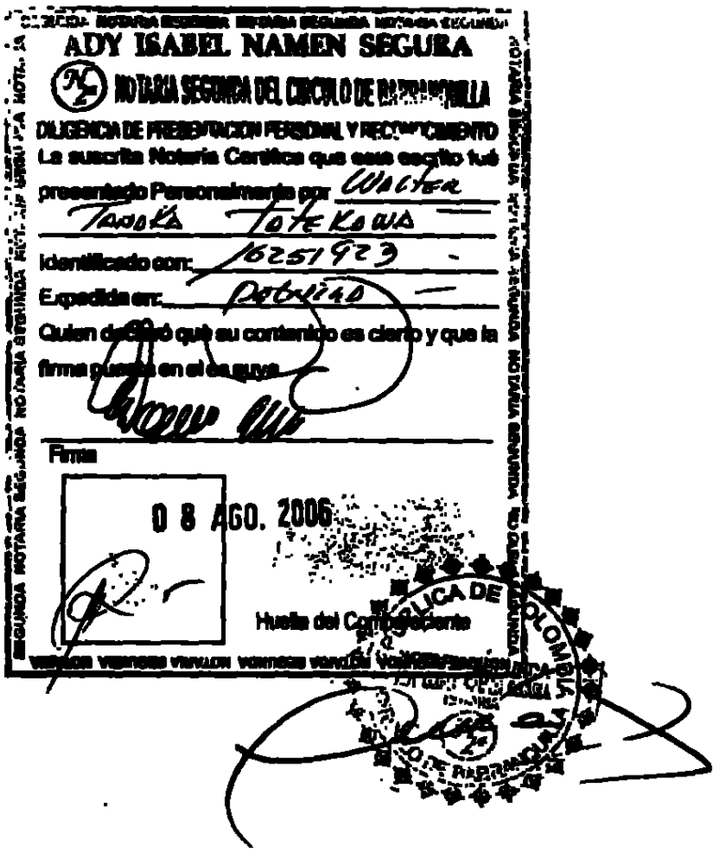
REINALDO PINILLA MORENO
C.C. 80'425.609 de Bogotá
T.P.A. 91563 del C.S. de la J.

PRESENTACION PERSONAL

En Bogotá, D.C. a 29 AGO 2006 se presentó en la Notaría Décima, cuyo titular es SERGIO FRANCO LEON REINALDO PINILLA MORENO

Con cédula No. 80425609 T.P. 91563 Expedida en USAQUEN y dijo que el anterior documento es cierto y que la firma es de su puño y letra. En constancia se firma

REPUBLICA DE COLOMBIA
NOTARIO DECIMO DE BOGOTA
SERGIO FRANCO LEON



ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que ese escrito fué presentado Personalmente por WALTER TAMARA TOKE KOWA

Identificado con: 1625923

Expedida en: PUTUMAYO

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

Firma

08 AGO. 2006

Huella del Compareciente

REPUBLICA DE COLOMBIA

NOTARIA SEGUNDA BARRANQUILLA

CAMARA DE COMERCIO DE BARRANQUILLA

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No. 1.190 del 22 de Julio de 1976, t rgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6.070 del libro respectivo, fue constituida la sociedad----------
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 1.307 del 28 de Junio de 1979, torgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10.039 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3.810 del 31 de Dic/bre de 1980, t rgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12.705 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad de responsabilidad limitada bajo al raz n s cial de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 3.755 del 10 de Nov/bre de 1983, torgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17.922 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3.615 del 06 de Dic/bre de 1996, torgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comerci , el 20 de Dic/bre de 1996 baj el No. 67.218 del libro respectivo, la s ciedad antes mencionada----------

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

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

PROCAPS S.A.----------
NIT: 890.106.527-5.

cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A
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C E R T I F I C A

Que por Escritura Pública No. 3.775 del 18 de Dic/bre de 1996, ot rgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67.704 del libro respectivo, la sociedad antes mencionada----------
cambio de razon social, por la denominacion PROCAPS S.A. ----------

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9.452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13.112	1981/05/06
1.464	1982/08/27	Notaria Unica de Soledad	15.533	1982/09/08
2.744	1983/08/18	Notaria Unica de Soledad	17.416	1983/08/26
3.826	1984/07/16	Notaria Unica de Soledad	19.554	1984/07/27
3.835	1985/08/26	Notaria Unica de Soledad	22.230	1985/09/04
2.260	1986/09/10	Notaria Unica de Soledad.	24.995	1986/09/15
1.849	1989/07/11	Notaria 2a. de Barranquilla.	33.909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36.101	1990/03/16
3.090	1991/12/17	Notaria 2a. de Barranquilla	43.993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48.428	1993/02/16
2.342	1993/07/28	Notaria 2a. de Barranquilla	50.582	1993/08/10
3.652	1993/11/09	Notaria 2a. de Barranquilla	51.798	1993/11/22
3.615	1996/12/06	Notaria 2a. de Barranquilla	67.218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67.704	1997/01/23
2.070	1997/07/17	Notaria 2a. de Barranquilla	70.627	1997/07/31
2.281	1997/08/04	Notaria 2a. de Barranquilla	70.813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80.628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91.502	2001/02/23
2.608	2001/10/05	Notaria 2a. de Barranquilla	95.771	2001/11/08
1.730	2004/07/29	Notaria 2. de Barranquilla	112.999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116.364	2005/03/10
1.613	2005/07/28	Notaria 2. de Barranquilla	119.322	2005/08/18

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:
PROCAPS S.A.----------
SIGLA: PROCAPS.
DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24.802.

C E R T I F I C A

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

CAMARA DE COMERCIO DE BARRANQUILLA

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
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NIT: 890.106.527-5.

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

C E R T I F I C A

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

C E R T I F I C A

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

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

PROCAPS S.A.----------
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prar, 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 gravamenes sobre bienes muebles e inmuebles; designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarroll 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 s cios, para lo cual podra inclusive constituir gravamenes reales sobre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2.000.000.000	**********2.000.000	**********1.000
Suscrito		
$**********1.220.000.000	**********1.220.000	**********1.000
Pagado		
$**********1.220.000.000	**********1.220.000	**********1.000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad c rresponderа 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 tras: Autorizar cualquier acto o contrato cuya cuantia sea superi r 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 transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los s cios, 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 representaci n legal de la sociedad y tendra las siguientes atribuci nes 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 l 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, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferi r al equivalente en pes s colombianos a doscientos cincuenta mil dolares de los

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CAMARA DE COMERCIO DE BARRANQUILLA

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Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta separadamente con el Presidente. El vicepresidente tendra las siguentes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la 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 interrogat rios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a cient cincuenta mil dolares de los Estados Unidos de America (US$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cu tas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravamenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatut s de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ell acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente c n el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar

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

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 inferi r al equivalente en pesos Colombianos a Cincuenta Mil dolares de l s Estados Unidos de America (US$50.000), liquidados a la tasa de cambi 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 gravamenes 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 según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.----------
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70.838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.----------
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87.250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*******7.463.982
2. Minski Gontovnik Meyer	CC.*******7.461.324
3. Minski Gontovnik Jose	CC.*******8.671.834

Suplentes

1. Minski Zilberblum Elliot	CC.******72.219.541
2. Minski Deitel Daniel	.****************
3. Minski Sharon	PA.*990.212.082.805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70.838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*******7.463.982

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CAMARA DE COMERCIO DE BARRANQUILLA

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Suplente del Presidente
Minski Minski Abraham CC.*********802.575
Vicepresidente
Minski Gontovnik Meyer CC.*******7.461.324
Suplente del vicepresidente
Minski Gontovnik Jose CC.*******8.671.834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comerci , el 12 de Febrero de 2001 bajo el No. 91.273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Gerente General.
Uribe Ochoa Guillermo Luis CC.******70.073.754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comerci , el 09 de Sep/bre de 2004 bajo el No. 113.263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Suplente del Gerente.
Tanaka Walter CC.******16.251.923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82.226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Revis r Fiscal Ppal.
Vargas Pertuz Ana Isabel CC.******32.696.645

C E R T I F I C A

Que según Acta N . 127 del 22 de Marz de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comerci ,

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NIT: 890.106.527-5.

el 29 de Mayo de 2000 bajo el No. 87.250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.******32.748.111

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001,otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se con fiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILIIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraci - nes tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o s - licitudes de informacion de las autoridades tributarias, aduaneras o cambiarias,en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial,amplio y suficiente,a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente sus criban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US$800.000.oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073. 754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.- 293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejer cici de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios,pedir la practica de pruebas,recibir notificaciones,interponer recursos y ejercer acciones contencioso administrativas y de tutela,transigir,conciliar,recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo c nciliatori o transaccional, judicial extrajudicial, cualquiera que sea su cuantia,los Apoderados deberan aportar la aut rizacion escrita del Representante Legal de la socie-

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dad. 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, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el 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 Exteri r 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

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 s ciedad firme las declaraci nes cambiarias a que este obligada PROCAPS S.A., a

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

suscribrir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el senor 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 senor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda t do tipo de requerimientos y/o solicitudes de informacion de las aut ridades 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, otorgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 18 de agosto del 2.005 bajo el No.2.913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C.No.7.463.928, en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a l s siguientes senores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancias y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US$800.000), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GRUPO A: MIRIAM RODRIGUEZ DIAZ, C.C.No. 41.473.569. GRUPO B: NELSON SUAREZ CHAVEZ, C.C.No.79.417.971.------.

C E R T I F I C A

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Que su última Renovación fue el: 29 de Marzo de 2006.

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

CAMARA DE COMERCIO DE BARRANQUILLA

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

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

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

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(71) Applicant *(for all designated States except US)*: LEK PHARMACEUTICAL AND CHEMICAL COMPANY D.D. [SI/SI]; Legal Affairs and Industrial Property, Verovskova 57, 1526 Ljubljana (SI).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: KERC, Janez [SI/SI]; Trebinjska 7, 1000 Ljubljana (SI). MATEJA, Salobir [SI/SI]; ul. 28. Maja 9, 1000 Ljubljana (SI). BAVEC, Sasa [SI/SI]; Mokinceva 15, 1000 Ljubljana (SI).

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(54) Title: ATORVASTATIN CALCIUM IN A PHARMACEUTICAL FORM, COMPOSITION THEREOF, AND PHARMACEUTICAL FORMULATION COMPRISING ATORVASTATIN CALCIUM

(57) Abstract: Atorvastatin calcium, the substance known by the chemical name (R-(R*,R*))-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-((phenylamino)carbonyl)-1H-pyrrole-1-heptanoic acid hemi calcium salt is known as HMG-CoA reductase inhibitor and is used as an antihypercholesterolemic agent. Atorvastatin in the pharmaceutical compositions available in the market, is usually prepared as its calcium salt since it enables atorvastatin to be conveniently formulated in the pharmaceutical formulations, for example, in tablets, capsules, powders and the like for oral administration. Atorvastatin calcium can exist in an amorphous form or in one of the at least four known crystalline forms (Form I, Form II, Form III and Form IV). Atorvastatin calcium is the substance which is sparingly soluble in water, with pKa 4,5, and it has been found that the crystalline forms are less soluble than the amorphous form, which may cause problems in bioavailability of atorvastatin in the body. The present invention solves the problem of providing therapeutic equivalence of atorvastatin pharmaceutical formulation regardless the form (crystalline, amorphous, mixture of both) of atorvastatin calcium used for its preparation.

Atorvastatin Calcium in a Pharmaceutical Form, Composition thereof, and Pharmaceutical Formulation comprising Atorvastatin Calcium

The present invention relates to atorvastatin calcium in a novel pharmaceutical form, a novel composition comprising atorvastatin calcium, and a pharmaceutical formulation comprising said atorvastatin calcium or said composition of atorvastatin calcium. Furthermore, the present invention relates to a process for the preparation of said pharmaceutical formulation and the use of said pharmaceutical formulation comprising atorvastatin calcium as active ingredient for the treatment of hypercholesterolemia, hyperlipidemia and the like.

Atorvastatin calcium, the substance known by the chemical name (R-(R*,R*))-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-((phenylamino)carbonyl)-1H-pyrrole-1-heptanoic acid hemi calcium salt is known as HMG-CoA reductase inhibitor and is used as an antihypercholesterolemic agent. Processes for the preparation of atorvastatin and key intermediates are disclosed in the United States Patent Numbers: 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,342,952 and 5,397,792. Atorvastatin in the pharmaceutical compositions available in the market, is usually prepared as its calcium salt since it enables atorvastatin to be conveniently formulated in the pharmaceutical formulations, for examples, in tablets, capsules, powders and the like for oral administration.

Atorvastatin calcium can exist in an amorphous form or in one of the at least four known crystalline forms (Form I, Form II, Form III and Form IV), which are disclosed in the patent applications WO 97/3958 and WO 97/3959. It is known that the amorphous forms of many pharmaceutical substances exhibit different dissolution characteristics and bioavailability patterns compared to the crystalline forms (Konno T., *Chem. Pharm. Bull.*, 1990;38;2003-2007). Bioavailability is one of the

key parameters for many therapeutic indications and is dependent on the form of the substance to be used in the pharmaceutical formulation. Processes for the crystallization and the preparation, respectively, of the amorphous substance are sometimes difficult to be performed, and as a product afford amorphous-crystalline mixtures with a changeable ratio of both forms, that is, crystalline form instead of amorphous form and vice versa. Since there are differences in the solubility among individual atorvastatin forms, as the patent application WO 97/3960 particularly emphasizes, also having an indirect impact on its bioavailability, it is very important to ensure uniformity of the substance being employed in a pharmaceutical formulation. Further, in the experiment it was observed that in acidic environment all atorvastatin calcium incorporated in a pharmaceutical formulation could not be dissolved because of the poor solubility of atorvastatin calcium and preparing a pharmaceutical formulation being constantly therapeutically equivalent was rendered impossible.

The problem of uniformity of atovarstatin calcium may be solved by employing the processes in its finalization which provide constant physical characteristics of the product. The problem occurs when atorvastatin calcium of mutually variable physical characteristics from several different sources is used for the preparation of a pharmaceutical formulation. Optionally the problem can be solved by preparing atorvastatin calcium as a crystalline form only (WO 97/3958 and WO 97/3959) and an amorphous form only (WO 97/3960, WO 01/42209, and Slovene patent application P-9900271), respectively, before it is incorporated in the formulation, which requires the use of an additional operation resulting in 5 to 10% loss. Since the patient should be provided with the drug being constantly therapeutically equivalent regardless to the form of atorvastatin calcium (regarding physical characteristics) incorporated in a pharmaceutical formulation, we have decided to solve the problem of the solubility of different forms of

atorvastatin calcium and consecutively its bioavailability at the level of the formulation. A further argument for this decision is the fact that atorvastatin calcium is an extremely expensive substance and all additional operations whereat a loss of the substance is possible considerably reduce the economical production process.

The patent literature describes atorvastatin calcium as an unstable substance and offers numerous solutions to provide a stable atorvastatin pharmaceutical formulation. Thus, for example, the stability of the formulation can be provided by the addition of a basic or a buffering agent to the formulation (WO 00/35425, WO 94/16603), namely by stabilizing the substance according to an analogous method described for pravastatin sodium in the patent application WO 01/93860. In order to prepare a stabilized amorphous substance, a combination of the methods disclosed in WO 01/93860, Slovene patent application P-9900271, and WO 01/42209 can be used. Insofar none of the described solutions on atorvastatin pharmaceutical compositions and formulations solves the problem of uniformity of atorvastatin calcium regarding the physical parameters (crystalline and amorphous form, respectively) and associated difficulties in providing therapeutic equivalence of atorvastatin calcium pharmaceutical formulation.

An object of the present invention is to solve the problem of providing therapeutic equivalence of atorvastatin calcium in a pharmaceutical form or comprised in a composition or a pharmaceutical formulation regardless the form (crystalline, amorphous, mixture of both) of atorvastatin calcium being used for the preparation thereof. The object of the present invention also relates to a pharmaceutical formulation containing an alkalising or a buffering substance which improves the bioavailability of atorvastatin by increasing its solubility and dissolution rate in aqueous solutions.

These and further objects are accomplished by the present invention as defined in the claims.

In a first aspect of the present invention the object may be accomplished by atorvastatin calcium in a pharmaceutical form having a pH equal to or greater than the pK_a+1 of atorvastatin calcium.

Moreover, in a second aspect of the present invention the object may also be accomplished by a composition comprising atorvastatin calcium providing a pH equal to or greater than the the pK_a+1 of atorvastatin calcium to an aqueous solution thereof.

Furthermore, according to a third aspect of the present invention the above object may further be accomplished by a pharmaceutical formulation comprising atorvastatin calcium as active ingredient, wherein the pharmaceutical formulation when dissolved in a liquid aqueous medium increases the pH of said medium to a pH equal to or greater than the pK_a+1 of atorvastatin calcium.

Further objects of the present invention can be achieved by preferred embodiments as set forth in the dependent claims.

The features of the present invention will become more apparent from the following description of the preferred embodiments.

The inventors surprisingly found that atorvastatin calcium in a pharmaceutical form according to the present invention or a composition comprising atorvastatin capable of providing a pH equal to or greater than the pK_a+1 of atorvastatin calcium to an aqueous solution improves the solubility of atorvastatin calcium dissolved therein such that it is negligible whether the amorphous or the crystalline form is dissolved.

More specifically, in the experiments the applicant has found that the solubility of atorvastatin calcium in aqueous

solutions is markedly improved at pH values equal to or greater than pKa+1 whereas surprisingly differences between atorvastatin calcium in crystal or amorphous form appear to be negligible. The pKa of atorvastatin's terminal carboxyl group is 4.5. Based on the above, it is preferred that when pH in the gastric microenvironment equal to or greater than pKa+1, more preferably pH of 6, is provided resulting from the composition or the pharmaceutical formulation according to the present invention comprising atorvastatin calcium, differences in the solubility will no longer be noticeable between different forms of atorvastatin calcium with different physical characteristics. The atorvastatin calcium forms having different physical characteristics which may be present in the composition or the pharmaceutical formulation according to the present invention can either be the amorphous form, the crystalline form or both forms simultaneously. Moreover, the present invention is not limited to these forms, but any physical form of atorvastatin calcium can be present in the composition or the pharmaceutical formulation of the present invention. More preferably, the amorphous atorvastatin calcium may be present in a form having a large specific surface, in particular as micronized amorphous atorvastatin calcium. Atorvastatin having a large specific surface has a further improved solubility characteristic.

In order to adjust the pH of the aqueous solution in the appropriate range, the composition or the pharmaceutical formulation according to the present invention optionally comprises a pH adjusting substance. The adjusting substance suitably used in the present invention is not specifically limited, however a substance selected from the group consisting of metal oxides, inorganic bases, organic bases, and salts of organic and inorganic acids is preferable. More preferably used pH adjusting substances are selected of the group consisting of oxides or hydroxides of alkaline or alkaline earth metals, in particular MgO, alkaline phosphate buffers, in particular

Na_3PO_4 and Na_2HPO_4, and organic amines, in particular tris(hydroxymethyl)methylamine.

In the present invention, the pharmaceutical formulation when used for a single administration and comprising atorvastatin calcium as active ingredient preferably comprises the pH adjusting substance in an amount of 0.2 to 2.0 mmol, and more preferably of 0.4 to 1.2 mmol. If the pH adjusting substance is comprised in the above specific range, the pH value of 900 ml aqueous HCl solution, more generally the pH value of an simulated gastric environment of the stomach, may be properly adjusted by single administration of the pharmaceutical formulation according to the present invention. Thus, an improved solubility characteristic of the atorvastatin calcium contained in the pharmaceutical formulation can be achieved, irrespective whether the atorvastatin calcium is contained in the amorphous and/or crystalline form.

Experiments

For *in vitro* simulation of preferred embodiments of atorvastatin calcium pharmaceutical formulations in acidic gastric environment of the stomach according to the present invention, the dissolution testing in a simulated gastric fluid having a pH value of about pH 3, and more specifically in 900 ml of aqueous 0.001M HCl solution, was performed. The concentration of dissolved atorvastatin was then measured at 10-minute intervals.

Four different formulations were prepared in form of tablets (A1, A2, A3 and A4; their composition is shown in Table 1), which were capable of providing different pH of the aqueous solution (obtained pH values of the solutions are shown in Table 2). Measurement results of the amount of dissolved atorvastatin in % are shown in Table 3.

Table 1

Composition	A1	A2	A3	A4
Atorvastatin amorphous, micronized*	20.00	20.00	20.00	20.00
Microcrystaline cellulose (Avicel PH112 or PH102)*	98.60	78.60	72.60	37.10
Lactose monohydrate (70-100 mesh)	34.80	34.80	34.80	20.00
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	9.60	9.60	9.60
Polysorbate 80	1.30	1.30	1.30	1.30
Hydroxypropyl cellulose (Klucel EF)	2.00	2.00	2.00	2.00
MgO	-	20.00	26.00	-
Na_2HPO_4	-	-	-	140.00
Microcrystalline cellulose (Avicel PH112)	71.90	71.90	71.90	48.20
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	9.60	9.60	19.60
Aerosil 200	1.20	1.20	1.20	1.20
Mg stearate	1.00	1.00	1.00	1.00
TOTAL	250.00	250.00	250.00	300.00
Demi water for granulation	100.00	70.00	70.00	-
Ethanol refined (96%)	-	-	-	50.00

*- Atorvastatin in the form of calcium salt in an equivalent amount, the difference is adjusted with an amount of microcrystalline cellulose

All quantities required for the preparation of one tablet are given in milligrams.

Table 2

	A1	A2	A3	A4
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	3.22	4.28	6.09	6.06
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	3.21	4.67	8.88	6.02

Table 3

	A1	A2	A3	A4
10 min	56.5	69.7	74.9	62.2
20 min	66.1	80.1	91.1	99.0
30 min	70.6	85.8	96.3	97.9
40 min	74.4	87.0	98.2	98.3
60 min	75.6	89.6	99.8	98.8

As evident from the measurements, all atorvastatin was dissolved advantageously in the case if the tablet was capable to increase the pH to a value that meets atorvastatin calcium's pKa+1, more specifically the pH of 900 ml of an aqueous 0.001M

HCl solution for three pH units, that is at least to pH 6. In these cases atorvastatin was dissolved at much faster rates.

In addition to improvement of the solubility, pKa+1 surprisingly also leveled the difference in solubility between atorvastatin calcium in a crystalline form and an amorphous form. To prove the above statement the granulations with the additions of different alkalising or buffering agents and different physical forms of atorvastatin calcium were prepared. Comparison of the release rate of atorvastatin from the granulations with added alkalising or buffering agents to the release rate of atorvastatin from the reference granulations with no added alkalising or buffering substances was carried out (Table 4). The pH values of solutions provided by different granulations are shown in Table 5. Measurement results of the amount of dissolved atorvastatin in % at different time intervals are shown in Table 6.

Table 4

Composition	AK1	AK2	AK3	AA1	AA2	AA3
Atorvastatin crystalline*	20.0	20.0	20.0	-	-	-
Atorvastatin amorphous*	-	-	-	20.0	20.0	20.0
Microcrystalline cellulose (PH102)*	71.3	71.3	71.3	71.3	71.3	71.3
Lactose monohydrate (70-100 mesh)	34.8	34.8	34.8	34.8	34.8	34.8
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6	9.6	9.6
Polysorbate 80	2.6	2.6	2.6	2.6	2.6	2.6
Hydroxypropyl cellulose (Klucel EF)	2.,0	2.0	2.0	2.0	2.0	2.0
Tris	110.0	-	-	110.0	-	-
Na_3PO_4	-	80.0	-	-	80.0	-
Microcrystalline cellulose (Avicel PH112)	67.9	67.9	67.9	67.9	67.9	67.9
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6	9.6	9.6
Aerosil 200	1.2	1.2	1.2	1.2	1.2	1.2
Mg stearate	1.0	1.0	1.0	1.0	1.0	1.0
Demi water for granulation	80.0	80.0	80.0	80.0	80.0	80.0

*- Atorvastatin in the form of Ca salt in an equivalent amount, the difference is adjusted with an amount microcrystalline cellulose

All quantities required for filling one capsule are given in milligrams.

Table 5

	AK1	AK2	AK3	AA1	AA2	AA3
pH (1 capsule in 900 ml aqueous 0.001M HCl solution) after 15 min	6.68	6.28	3.14	5.81	6.28	3.20
pH (1 capsule in 900 ml aqueous 0.001M HCl solution) after 30 min	6.95	6.72	3.15	5.68	6.30	3.24

Table 6

	AK1	AK2	AK3	AA1	AA2	AA3
10 min	64.6	49.9	31.8	75.9	50.8	38.7
20 min	76.4	63.4	44.5	82.6	62.1	53.4
30 min	81.0	72.3	51.4	83.6	68.5	61.5
40 min	84.2	77.3	55.8	83.9	72.8	66.6

From the obtained results it is evident that the percentage difference in the amount of dissolved amorphous and crystalline atorvastatin calcium was approximately 20% when the granulation without added alkalising or buffering substance was used, and a difference appeared minimal (< 5%) when a buffering substance was added.

It was tried to additionally improve the solubility of amorphous atorvastatin calcium by enlarging the specific surface area of particles of the amorphous substance. Six different granulations were prepared in the same manner as in the previous experiment, the only difference being instead of crystalline atorvastatin, micronized amorphous atorvastatin calcium (AAM1, AAM2 and AAM3 samples) was used having several times larger specific surface area of the particles compared to nonmicronized. The pH values provided by the granulations are shown in Table 7. Measurement results of the amount of dissolved atorvastatin in % at different time intervals are shown in Table 8.

Table 7

	AAM1	AAM2	AAM3	AA1	AA2	AA3
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	6.80	6.40	3.12	5.81	6.28	3.20
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	6.76	6.44	3.30	5.68	6.30	3.24

Table 8

	AAM1	AAM2	AAM3	AA1	AA2	AA3
10 min	85.9	93.9	41.5	75.9	50.8	38.7
20 min	95.8	94.2	55.9	82.6	62.1	53.4
30 min	98.4	93.9	63.8	83.6	68.5	61.5
40 min	99.3	94.0	68.9	83.9	72.8	66.6

From the obtained results it is evident that there was practically no difference in the amount of dissolved amorphous and amorphous micronized atorvastatin when the granulation without added buffering agent was used, and the difference increased to more than 15 - 20 % when a buffering agent was added.

The aforementioned experiments surprisingly showed that it was possible to provide therapeutic equivalence of atorvastatin calcium in a pharmaceutical form, a composition thereof as well as pharmaceutical formulations regardless which form (crystalline, amorphous, mixture of both) of atorvastatin calcium was used for their preparation. Of paramount importance for providing the therapeutic equivalence is the capability of the atorvastatin calcium, the composition thereof, and the pharmaceutical formulation according to the present invention to provide a pH equal to or greater than the pK_a+1 of atorvastatin calcium to an aqueous solution. In a preferred embodiment atorvastatin calcium, the compsoitions and the formulation of the present invention have the capability to increase the pH of 900 ml aqueous 0.001M HCl solution to pH values equal to or greater than pKa+1 or more, in particular pH 6 or more.

The other surprising finding was that the dissolved amount of micronized amorphous atorvastatin calcium in the granulation with added alkalising or buffering substance is approximately for 15% greater than in case of nonmicronized atorvastatin calcium. Here the most surprising fact is that an increase of a specific surface of the particles itself does not have an impact on the improvement of the solubility, as the solubility

of micronized and nonmicronized amorphous atorvastatin calcium in the granulation with no added alkalising or buffering substance is equivalent.

The pharmaceutical formulation, which is the object of the present invention, may contain, in addition to atorvastatin calcium, one or more fillers such as microcrystalline cellulose, lactose, sugars, starches, modified starch, mannitol, sorbitol and other polyols, dextrin, dextran and maltodextran, calcium carbonate, calcium phosphate and/or hydrogen phosphate, sulfate, one or more binders such as lactose, starches, modified starch, dextrin, dextran and maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxy methylcellulose, sodium carboxy methylcellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone, magnesium aluminum silicate, one or more disintegrating agents such as cross-linked sodium carboxy methylcellulose, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl starch, starches and microcrystalline cellulose, magnesium aluminum silicate, polyacrylin potassium, one or more different glidants such as magnesium, calcium and zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax, silicon dioxide, one or more buffering substances such as sodium citrate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulfate, magnesium carbonate, potassium citrate, potassium sorbate, sodium ascorbate, benzoate, hydrogen carbonate, hydrogen phosphate, or one or more basic substances such as MgO, MgOH, NaOH, $Ca(OH)_2$, tromethamine, Al Mg silicate, lauryl sulfate. If required, the formulation may also include surfactants and other conventional ingredients for solid pharmaceutical formulations such as coloring agents, lakes, flavoring agents and adsorbents. As surfactants the following may be used: ionic surfactants such as sodium lauryl sulfate or

non-ionic surfactants such as different poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural or synthesized lecithins, esters of sorbitant and fatty acids (such as Span® (Atlas Chemie)), esters of polyoxyethylenesorbitan and fatty acids (such as Tween® (Atlas Chemie)), polyoxyethylated hydrogenated castor oil (such as Cremophor® (BASF)), polyoxyethylene stearates (such as Myrj (Atlas Chemie)) or cationic surfactants such as cetyl pyridine chloride or any combination of the herein abovementioned surfactants.

The pharmaceutical formulations of the present invention may be provided either as solid pharmaceutical formulations, such as powders, granules, tablets, or capsules, for example, or as liquid pharmaceutical formulations, preferably filled in capsules.

The solid pharmaceutical formulations according to the present invention, may be prepared as described below:

- The mixture of the active ingredient, a filler, a binder, an alkalising or buffering substance, a disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations is homogenized employing suitable mixers, the mixture is compacted using suitable compaction machines or slugged on slugging machines, the compacts or slugs are triturated and/or sieved, fillers, disintegrating agents, buffering substances, glidants, lubricants and other conventional inactive ingredients for tablets or capsules are added, and re-homogenized. The resulting mixture is compressed into tablets or filled into capsules.

- The mixture of the active ingredient, a filler, a binder, an alkalising or buffering substance, a disintegrating agent and if required a surfactant and other conventional

ingredients for solid pharmaceutical formulations are homogenized employing suitable mixers, glidants and lubricants are added and re-homogenized. The resulting mixture is compressed into tablets or filled into capsules.

- The mixture of the active ingredient, a filler, a binder, an alkalising or buffering substance, a disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations are homogenized employing suitable mixers, granulated with a suitable solvent such as water, ethanol, methanol, isopropyl alcohol, n-butyl alcohol, acetone, diethylether, ethylacetate, isopropyl acetate, methyl acetate, dichloromethane, chloroform, mixtures of these solvents such as ethanol and acetone, methanol and acetone, dichloromethane and methanol, and the mixtures thereof. The resulting granulation is dried in suitable dryers such as standard tray dryers, fluidized bed dryers, vacuum and microwave dryers, at a temperature not exceeding 60°C. To the dried granulation, glidants, disintegrating agents, alkalising or buffering substances, glidants and lubricants are added and if required other conventional ingredients for solid pharmaceutical formulations. The resulting mixture is re-homogenized and compressed into tablets or filled into capsules.

Optionally, tablets are film-coated.

The present invention is illustrated but in no way limited by the following examples.

EXAMPLES

Examples 1-2

Tablets with added MgO or Na_2PHO_4

The ingredients, listed in the table below, were homogenized in a mixer and granulated with water and ethanol, respectively. The resulting granulation was dried in a vacuum dryer at a temperature not exceeding 60°C.

Composition	A3	A4
Atorvastatin amorphous, micronized*	20.00	20.00
Microcrystalline cellulose (Avicel PH112 or PH102)*	72.60	37.10
Lactose monohydrate (70-100 mesh)	34.80	20.00
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	9.60
Polysorbate 80	1.30	1.30
Hydroxypropyl cellulose (Klucel EF)	2.00	2.00
MgO	26.00	-
Na_2HPO_4	-	140.00
Demi water for granulation	70.00	-
Ethanol refined for granulation (96%)	-	50.00

*- Atorvastatin in the form of Ca salt in an equivalent amount, the difference is adjusted with an amount of microcrystalline cellulose

All quantities are given in milligrams (for one tablet). The quantity of the prepared granulation was sufficient for the preparation of 1000 units of 250 mg tablets.

To the dried granulation the following was added:

Microcrystalline cellulose (Avicel PH112)	71.90	48.20
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	19.60
Aerosil 200	1.20	1.20
Mg stearate	1.00	1.00

The resulting mixture was re-homogenized and compressed into tablets. The pH values provided by one tablet in 900 ml of aqueous 0.001M HCl solution were the following:

	A3	A4
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	6.09	6.06
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	8.88	6.02

Examples 3-6

Capsules with amorphous and crystalline, respectively, atorvastatin calcium with added Tris and Na_3PO_4, respectively

The ingredients, listed in the table below, were homogenized in a mixer and granulated with water and ethanol, respectively. The resulting granulation was dried in a vacuum dryer at a temperature not exceeding 60°C.

Composition	AK1	AK2	AA1	AA2
Atorvastatin crystalline*	20.0	20.0	-	-
Atorvastatin amorphous*	-	-	20.0	20.0
Microcrystalline cellulose (PH102)*	71.3	71.3	71.3	71.3
Lactose monohydrate (70-100 mesh)	34.8	34.8	34.8	34.8
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6
Polysorbate 80	2.6	2.6	2.6	2.6
Hydroxypropyl cellulose (Klucel EF)	2.0	2.0	2.0	2.0
Tris	110.0	-	110.0	-
Na_3PO_4	-	80.0	-	80.0
Demi water for granulation	80.0	80.0	80.0	80.0

All quantities required for preparation of the granulation for one capsules are given in milligrams. The quantity of the prepared granulation was sufficient for filling 1000 capsules.

To the dried granulation the following was added:

Microcrystalline cellulose (Avicel PH112)	67.9	67.9	67.9	67.9
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6
Aerosil 200	1.2	1.2	1.2	1.2
Mg stearate	1.0	1.0	1.0	1.0

The resulting mixture was re-homogenized and compressed into tablets. The pH values provided by one tablet in 900 ml of aqueous 0.001M HCl solution were the following:

	AK1	AK2	AA1	AA2
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	6.68	6.28	5.81	6.28
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	6.95	6.72	5.68	6.30

Optionally, used atorvastatin could be micronized or prepared according to some other method to enlarge a specific surface area of the particles (e.g., grinding)

184 37

Claims:

1. Atorvastatin calcium in a pharmaceutical form of an aqueous solution having a pH equal to or greater than the pK_a+1 of atorvastatin calcium.

2. A composition comprising atorvastatin calcium providing a pH equal to or greater than the pK_a+1 of atorvastatin calcium to an aqueous solution thereof.

3. The composition according to claim 2 comprising further a pH adjusting substance.

4. The composition according to claim 3 wherein the pH adjusting substance increases the pH of an aqueous solution equal to or grater than the pK_a+1 of atorvastatin calcium.

5. The composition according to any of the claims 2 to 4 wherein the pH is adjusted to 6 or more.

6. The composition according to any of the claims 2 to 5, wherein the pH adjusting substance is at least on substance selected from alkalising and buffering substances.

7. A pharmaceutical formulation comprising atorvastatin calcium as active ingredient,

characterized in that

the pharmaceutical formulation when dissolved in a liquid aqueous medium increases the pH of said medium to a pH equal to or greater than pK_a+1 of atorvastatin calcium.

8. The pharmaceutical formulation according to claim 7, wherein the atorvastatin calcium is present in the formulation in different physical forms.

9. The pharmaceutical formulation according to claim 7 or 8, wherein the atorvastatin calcium is present in the formulation in a crystalline and/or amorphous form at the same time.

10. The pharmaceutical formulation according to any of the claims 7 to 9, wherein the atorvastatin calcium comprises amorphous atorvastatin calcium having a large specific surface of the particles.

11. The pharmaceutical formulation according to claim 10, wherein the atorvastatin calcium comprises micronized amorphous atorvastatin calcium.

12. The pharmaceutical formulation according to any of the claims 7 to 9, wherein the atorvastatin calcium comprises crystalline atorvastatin calcium.

13. The pharmaceutical formulation according to any of the claims 7 to 12, wherein the formulation provides in the simulated gastric fluid of pH of 3 a pH of equal to or greater than pK_a+1.

14. The pharmaceutical formulation according to claim 13, wherein the formulation provides a pH of 6.

15. The pharmaceutical formulation according to any of the claims 7 to 14, wherein the amount of the pH adjusting substance is adjusted in the formulation such that a single administration increases the pH of 900 ml aqueous HCl solution having a pH of about 3, in particular 900 ml of a 0.001 M HCl solution, to a pH equal to or greater than pK_a+1 or more.

16. The pharmaceutical formulation according to any of the preceding claims, wherein the pH adjusting substance is contained in the pharmaceutical formulation in an amount of 0.2 to 2.0 mmol, in particular in an amount of 0.4 to 1.2 mmol.

17. The pharmaceutical formulation according to any of the claims 7 to 16, wherein the pH adjusting substance is selected from the group of metal oxides, inorganic bases, organic bases, and salts of organic and inorganic acids.

18. The pharmaceutical formulation according to any of the claims 7 to 17, wherein the pH adjusting substance is selected from the group consisting of metal oxides, oxides or hydroxides of the alkaline or alkaline earth metals, in particular MgO, alkaline phosphate buffers, in particular Na_3PO_4 and Na_2HPO_4, and organic amines, in particular tris(hydroxymethyl)methylamine.

19. The pharmaceutical formulation according to any of the claims 7 to 18 in the form of a powder, granules, a tablet or a capsule.

20. The pharmaceutical formulation according to any of the claims 7 to 19 comprising further one or more components selected from the group of fillers, binders, buffering substances, basic substances, surfactants and other pharmaceutically acceptable ingredients.

21. A process for the preparation of a pharmaceutical formulation comprising atorvastatin calcium as active ingredient,

characterized by the following steps:

(a) mixing the active ingredient with at least one component selected from the group consisting of alkalising and/or buffering substances, fillers, binders, disintegrants, and surfactants;

(b) homogenizing the above mixture;

(c) adding additional ingredients to the above mixture;

(d) re-homogenizing the resulting mixture; and

(e) final processing the re-homogenized mixture in administrable form.

22. The process according to claim 21 wherein the final processing step (e) is compressing the re-homogenized mixture into tablets.

23. The process according to claim 21 wherein the final processing step (e) is filling the re-homogenized mixture into capsules.

24. The process according to any of the claims 21 to 23, further comprising the steps of:

(f) compacting the mixture after homogenization; and

(g) further processing including triturating and/or sieving the compacted mixture before adding additional ingredients.

25. The process according to any of the claims 21 to 24, further comprising the steps of:

(h) granulating the homogenisate obtained in step (b) with granulation liquid; and

(i) drying the obtained granulate before adding additional ingredients.

26. The process according to claim 24 or 25, wherein the additional ingredients are selected from the group consisting of fillers, binders, disintegrants, alkalising agents, and glidants.

27. The process according to any of the claims 21 to 26, wherein the addition of the pH adjusting substance is adjusted such that a single administration of the formulation increases the pH of the acidic environment to a pH equal to or greater than pK_a+1 of atorvastatin calcium.

28. The process according to claim 27, wherein the addition of the pH adjusting substance is adjusted such that a single administration of the formulation increases the pH of the acidic environment to a pH of 5.5 or more.

29. The process according to any of the claims 21 to 28 for the preparation of a solid formulation according to any of the claims 7 to 20.

30. The use of a solid formulation according to any of the claims 7 to 20 or of a solid formulation prepared according to any of the claims 21 to 29 for the treatment of hypercholesterolemia and hyperlipidemia.

ANEXO 2

US005686104A

United States Patent [19]

Mills et al.

[11] Patent Number: 5,686,104

[45] Date of Patent: Nov. 11, 1997

[54] **STABLE ORAL CI-981 FORMULATION AND PROCESS OF PREPARING SAME**

[75] Inventors: Nancy Mills, Mt. Arlington; Nouman A. Muhammad, Long Valley; Jay Weiss, East Brunswick; Russell U. Nesbitt, Somerville, all of N.J.

[73] Assignee: Warner-Lambert Company, Morris Plains, N.J.

[21] Appl. No.: 246,919

[22] Filed: May 20, 1994

Related U.S. Application Data

[63] Continuation of Ser. No. 5,708, Jan. 19, 1993, abandoned.

[51] Int. Cl.[6] A61K 9/16; A61K 9/20; A61K 9/48; A61K 47/02

[52] U.S. Cl. 424/451; 424/465; 424/683; 424/692; 424/693; 424/715; 424/489; 514/824

[58] Field of Search 424/451, 454, 424/465, 715, 683, 692, 693; 514/824

[56] References Cited

U.S. PATENT DOCUMENTS

4,681,893	7/1987	Roth	514/422
5,030,447	7/1991	Mills et al.	514/422

FOREIGN PATENT DOCUMENTS

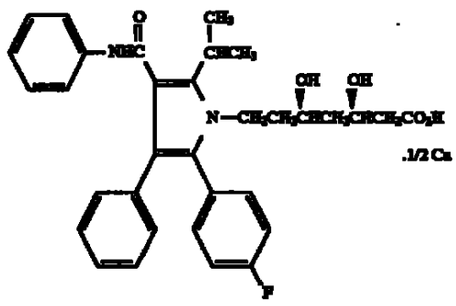
409281A1	1/1991	European Pat. Off. .

Primary Examiner—Edward J. Webman

Attorney, Agent, or Firm—Michael J. Atkins

[57] ABSTRACT

An oral pharmaceutical composition is provided for treating hypercholesterolemia or hyperlipidemia containing an advantageous formulation for stabilizing the HMG-CoA coenzyme A inhibitor, CI-981 Hemi-Calcium, of formula (IA)



with effective amounts of calcium carbonate. A method for preparing a CI-981 stabilizing composition is described.

23 Claims, No Drawings

STABLE ORAL CI-981 FORMULATION AND PROCESS OF PREPARING SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. Ser. No. 08/005,708 filed Jan. 19, 1993, now abandoned.

FIELD OF THE INVENTION

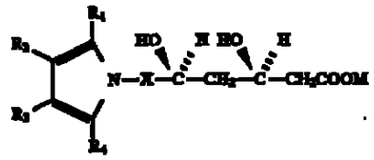
The present invention relates to stable oral pharmaceutical formulations of acid-sensitive substituted pyran ring-opened acid forms of substituted pyrrolyl carboxamides useful in the treatment of hypercholesterolemia or hyperlipidemia. A method for the preparation of such formulations is also described.

BACKGROUND OF THE INVENTION

Hypercholesterolemia and hyperlipidemia, conditions of excessively high levels of blood cholesterol and lipids, are well recognized risk factors in the onset of atherosclerosis and coronary heart disease. The blood cholesterol pool is generally dependent on dietary uptake of cholesterol from the intestine and biosynthesis of cholesterol throughout the body, especially the liver. Cholesterol is an indispensable component of virtually all cell membrane systems, as well as a precursor of a variety of steroid hormones and bile acids.

It is well known that inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), an important enzyme catalyzing the intracellular synthesis of cholesterol, will bring about reduced levels of blood cholesterol, especially in terms of the low density lipoprotein form of cholesterol. Therefore, HMG-CoA reductase enzyme inhibitors are considered potentially useful as hypocholesterolemic or hypolipidemic agents.

Certain trans-6-[2-(3 or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and corresponding pyran ring-opened hydroxy acids derived therefrom have been described in U.S. Pat. No. 4,681,893 to Roth as potent inhibitors of HMG-CoA reductase which description is herewith incorporated by reference in the present specification. The pyran ring-opened hydroxy acids which are intermediates in the synthesis of the lactone compounds can be used as free acids or as pharmaceutically acceptable metal or amine salts. In particular, these compounds can be represented by the formula I below:



(I)

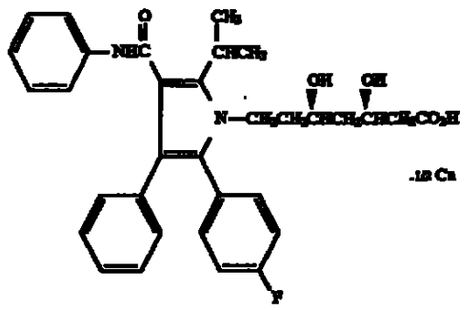
wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$;

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other of R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl; and M is a pharmaceutically acceptable salt, which includes a pharmaceutically acceptable metal salt or a pharmaceutically acceptable amine salt.

Among the stereo-specific isomers one particular compound having HMG-CoA reductase inhibitory activity, CI-981 Hemi-Calcium, is currently under development for the treatment of moderate to severe familial or nonfamilial hypercholesterolemia (Type IIa). This most preferred compound characterized is the ring-opened form of (2R-trans)-5-(4-fluorophenyl)-2-(1 methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, namely, the enantiomer [R-(R*, R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl)]-1H-pyrrole-1-heptanoic acid hemicalcium salt. Its chemical structure may be represented by formula IA:



(IA)

.1/2 Ca

The specific isomer (CI-981) has been described in U.S. Pat. No. 5,273,995.

However, these compounds are unstable in that they are susceptible to heat, moisture, low pH environment, and light. In an acidic environment, in particular, the hydroxy acids will degrade to lactone. In addition, the hydroxy acids will decompose rapidly when exposed to UV or fluorescent light.

When packaged in the form of tablets, powders, granules, or within capsules, the compounds may be further destabilized by contact with the molecular moieties of other components. Since pharmaceutical dosage components such as binders, diluents, antiadherents, surfactants and the like may adversely interact with the active ingredient compound, a stabilizing means is required for effective pharmaceutical dosages.

Therefore, it is an object of the present invention to provide a stable solid peroral pharmaceutical formulation comprising substituted pyrrolyl substituted pyran ring-opened hydroxy acids for therapy of hypercholesterolemia or hyperlipidemia. More particularly, it is the object of the present invention to provide a stable solid peroral pharmaceutical formulation comprising a HMG CoA reductase inhibitor, such as the aforedescribed CI-981 Hemi-Calcium, as active ingredient.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a pharmaceutical formulation characterized by improved stability of a

7-substituted pyrrolyl-3,5-dihydroxyheptanoic acid salt as active ingredient combined with at least one pharmaceutically acceptable stabilizing additive for peroral treatment of hypercholesterolemia or hyperlipidemia.

An aspect of the present invention is to provide a stable oral pharmaceutical formulation for the treatment of hypercholesterolemia or hyperlipidemia comprising as active ingredient, a HMG-CoA reductase enzyme inhibitor according to Formula (I), as defined above, which is stabilized by combination with at least one pharmaceutically acceptable metal salt additive.

Another aspect of the present invention is to provide a stable oral pharmaceutical formulation for the treatment of hypercholesterolemia or hyperlipidemia comprising, as an active ingredient, a HMG-CoA reductase inhibitor such as CI-981 Hemi-Calcium, namely, the enantiomer [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl)]-1H-pyrrole-1-heptanoic acid, hemicalcium salt, having the proposed isomeric structural Formula (IA) stabilized by a combination with at least one pharmaceutically acceptable alkaline earth metal salt such as calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate or aluminum magnesium hydroxide.

Further, a preferred embodiment of the present invention provides a stable peroral pharmaceutical formulation for the treatment of hypercholesterolemia or hyperlipidemia comprising the HMG-CoA reductase inhibitor, CI-981 Hemi-Calcium, having the proposed structure according to the above-described structural Formula (IA) combined with calcium carbonate as stabilizing additive.

Further, a preferred embodiment of the present invention provides a stable oral pharmaceutical formulation for the treatment of hypercholesterolemia or hyperlipidemia comprising the HMG-CoA reductase inhibitor, CI-981 Hemi-Calcium, as active ingredient in a composition comprising, in addition to the stabilizing additive calcium carbonate, at least one other ingredient such as a binder, diluent, disintegrant, surfactant, and, optionally, antioxidant.

More specifically, the present invention provides a stable solid oral pharmaceutical composition wherein the active ingredient dosage is between about 1% and about 50% by weight of the composition.

The present invention also provides a stable solid oral pharmaceutical composition containing about 5% to about 75% of the stabilizer calcium carbonate by weight of the composition.

Another preferred embodiment of the present invention is a stable solid oral pharmaceutical composition comprising in addition to the active and the stabilizing ingredients, cited above, by weight, between about 5% and about 75% microcrystalline cellulose; between about 1% and about 80% of hydrous lactose; between about 1% and about 15% of croscarmellose sodium; between about 0.5% and about 6% hydroxypropyl cellulose; between about 0.1% and about 4% of Tween 80; between about 0.25% and about 2% of magnesium stearate; and optionally between about 0.0% and about 3% of sodium ascorbate or butylated hydroxyanisole of the total solid composition.

The present invention is also directed to a method of preparing a stable solid composition of the active ingredient according to Formula (I) comprising a stabilizing additive, for peroral therapy of hypercholesterolemia or hyperlipidemia.

A preferred embodiment of the present invention also provides a method for preparing the solid oral composition, including stabilizing the active ingredient, CI-981 Hemi-Calcium, according to Formula (IA) with calcium carbonate and admixing a binder, a diluent, a disintegrant, a surfactant, and optionally an antioxidant.

DETAILED DESCRIPTION OF THE INVENTION

The pyran ring-opened hydroxy acid corresponding to certain trans-6-[2-(3 or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones can be useful inhibitors of HMG-CoA reductase and may be used in their free acid form. Both lactone and free acid forms can be prepared in accordance with the process described in U.S. Pat. No. 4,681,893, which is incorporated by reference therefor. The free acid can be prepared by hydrolysis of the lactone form or by treatment of the salt with cationic exchange resin (H^+ resin) and evaporating the water portion. These free acids also react to form pharmaceutically acceptable metal or amine salts. The term "pharmaceutically acceptable metal salt" contemplates sodium, potassium, lithium, calcium, magnesium, aluminum, iron, or zinc salts. The term "pharmaceutically acceptable amine salt" contemplates salts formed by reaction with ammonium hydroxide or organic amine salt or for example methylglucamine, choline, arginine, 1-deoxy-2-(methylamino)-D-glucitol and the like.

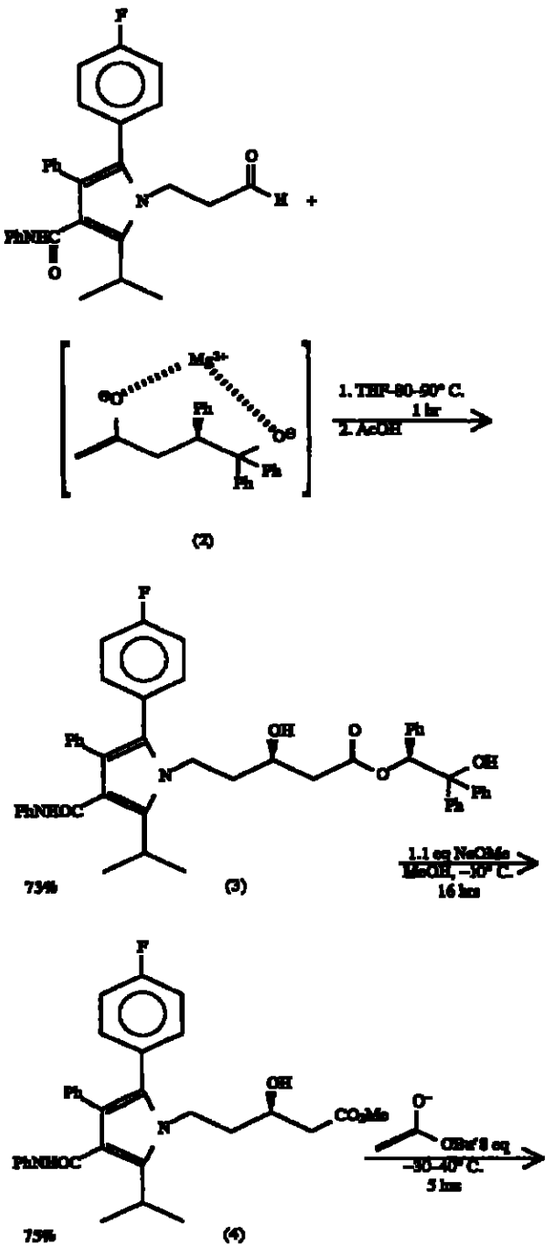
Insofar as the hydroxy acid compounds according to formula I or metal or amine salts thereof are HMG-CoA reductase inhibitors they may be useful in the treatment of hypercholesterolemia or hyperlipidemia. The compound of particular interest is the HMG-CoA reductase enzyme inhibitor, CI-981 Hemi-Calcium, Formula (IA), which is presently under development as a drug for treatment of hypercholesterolemia or hyperlipidemia.

The preferred compounds according to the present invention, especially the compound CI-981 or [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt, inhibit the biosynthesis of cholesterol as measured in the CSI screen assay disclosed in U.S. Pat. No. 4,681,893, which is incorporated by reference. More particularly, the level of HMG-CoA reductase enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed. The rat livers are dissected and homogenized, and the incorporation of cholesterol - ^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and denoted as an IC_{50} value. The activity data of representative examples of the compound CI-981 Hemi-Calcium, its enantiomer and the racemate of both compounds have been disclosed in the aforementioned U.S. Pat. No. 5,273,995, which are incorporated herein.

Compound	IC_{50} (nanomolar/liter)
[R-(R*,R*)] Isomer (CI-981 Hemi-Calcium)	0.0044
[S-(R*,R*)] Isomer	0.44
Racemate	0.045

The most preferred compound of the present invention, CI-981 (structural Formula IA), is the enantiomer [R-(R*R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1

H-pyrrole-1-heptanoic acid, hemicalcium salt. This chiral form can be synthesized from known starting materials or from materials prepared according to methods analogous to known processes in accordance with the scheme 2 of the copending patent application recited above and incorporated by reference herein, as follows:



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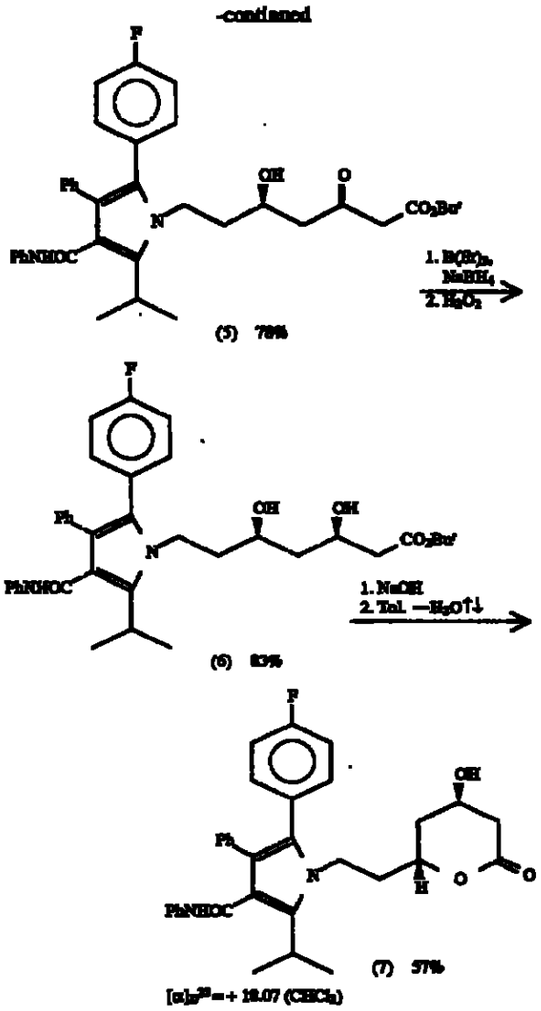


In addition, the preferred chiral form can be prepared from a racemic mixture prepared by the methods described in U.S. Pat. No. 4,681,893, especially examples 1 and 2 which description is incorporated by reference therefor.

Reference of the racemate and separation of the preferred isomer can be performed in accordance with the methodology for chiral synthesis disclosed in copending U.S. patent application Ser. No. 07,660,976, as illustrated in the Examples 1–5, which is incorporated herein by reference therefor.

The present invention provides a pharmaceutical composition containing hypocholesterolemic or hypolipidemic compounds according to preferredly Formula (I) or more preferredly Formula (IA). The prefered effective stereoisomeric compounds of the present invention are administered to the patient at adult dosage levels of from approximately 10 to 500 mg per day, or from about 0.1 to about 8.0 mg/kg body weight per day. More preferred daily dosages range from about 0.5 to about 1.0 mg/kg. The unit dosage treat-

ment embodiment provided by the present invention for oral or parenteral administration may be varied or adjusted from 10 to 500 mg, preferably from 20 to 100 mg depending on potency or application. .

Since the hydroxy acid compounds according to formula I are susceptible to degradation to the lactone form in an acidic environment, it has been necessary to stabilize their structural integrity in pharmaceutical formulations. Moreover, the compounds have been determined to decompose rapidly under the impact of UV and fluorescent light.

For the purpose of stable oral preparations of the present invention, pharmaceutically acceptable inert carriers can be either solid or liquid. The most preferred embodiment of the present invention provides for an oral solid formulation which may include powders, tablets, dispersible granules, capsules, and cachets. A solid carrier may be one or more substances which can also act as diluents, flavoring agents, binders, or tablet disintegrating agents. Encapsulating materials are also within the scope of the present invention.

In powdered preparations, the carrier is preferably a solid which is finely divided in a homogeneous mixture with the finely divided active ingredient. In tablets, the active component is blended with the carrier material with binding properties that facilitate compacting, shaping and sizing as desirable. Oral powders or tablets according to the present invention are generally designed to contain between about 1% to about 50% by weight of the active ingredient.

As is usual in the art, pharmaceutical preparations are in suitable unit dosage form, which can be a capsule, cachet or tablet, or any number thereof, as appropriate. Dosages are held to be within the skill of the art and may vary with the particular requirements and bioavailability of the active ingredient.

In practice, use of the salt form amounts to use of the acid or lactone form. Appropriate pharmaceutically acceptable salts within the scope of the invention are those derived from bases such as sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, 1-deoxy-2-(methylamino)-D-glucitol, magnesium hydroxide, zinc hydroxide, aluminum hydroxide, ferrous or ferric hydroxide, ammonium hydroxide or organic amines such as N-methylglucamine, choline, arginine and the like. Preferably, the lithium, calcium, magnesium, aluminum and ferrous or ferric salts are prepared from the sodium or potassium salt by adding the appropriate reagent to a solution of the sodium or potassium salt, i.e., addition of calcium chloride to a solution of the sodium or potassium salt of the compound of the formula I will give the calcium salt thereof.

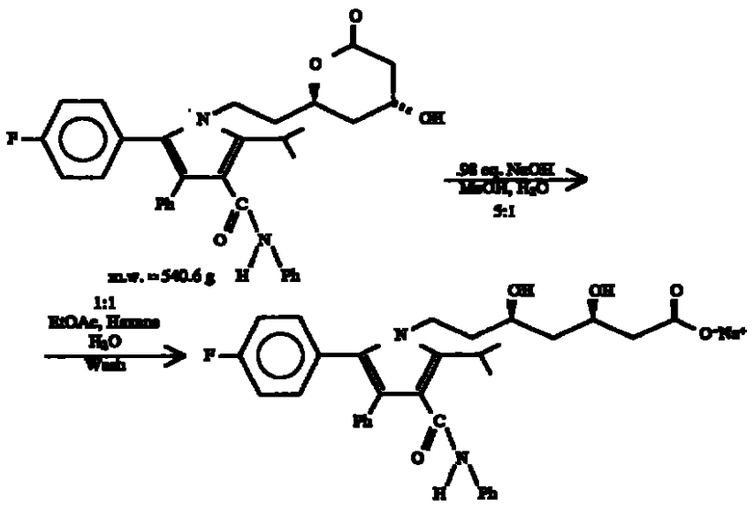
The active hydroxy acid metal salt ingredient of the present invention which may be an isoeneric compound with a structure according to Formula (I) or, preferredly, Formula (IA) can be prepared from sodium salt or lactone as illustrated in Example A, below.

EXAMPLE A

Calcium Salt from Sodium Salt and/or Lactone

One mole lactone (540.6 g) is dissolved in 5 L of MeOH; after dissolution 1 L H_2O is added. While stirring, one equivalent NaOH is added and the reaction is followed by HPLC until 2% or less lactone and methyl ester of the diolacid remains (one cannot use an excess of NaOH, because $Ca(OH)_2$ will form on addition of $CaCl_2$). Usually NaOH is charged as caustic (51.3 ml, 0.98 eq.) or as pellets (39.1 g, 0.98 eq.).

The above procedure is shown as follows:

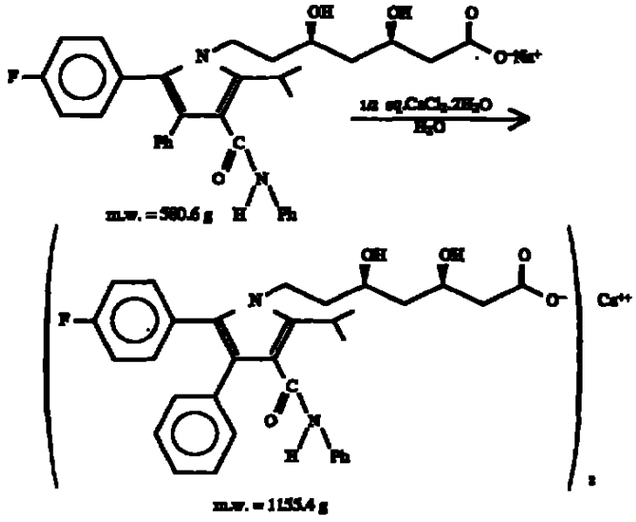


The abbreviation "Ph" is for the term phenyl group. Upon completion of hydrolysis, 10 L H_2O are added, then the product is washed at least two times with a 1:1 mixture of EtOAc/Hexane. Each wash should contain 10 L each of EtOAc/Hexane. If sodium salt is pure, 15 L of MeOH are added. If it is impure and/or contains color, 100 g of G-60 charcoal are added, the mixture is stirred for two hours, filtered over supercel, and washed with 15 L MeOH. An assay analysis (weight per volume, %) is performed on the reaction mixture by HPLC, to determine the exact amount of salt in solution.

Subsequently, about ½ equivalent or a slight excess of $CaCl_2 \cdot 2H_2O$ (73.5 g) is dissolved in 20 L H_2O. Both the reaction mixture and the $CaCl_2$ solution are heated to 60° C. $CaCl_2$ solution is added slowly, with high agitation. After complete addition, the reaction mixture is cooled slowly to 15° C. and filtered. The filter cake is washed with 5 L H_2O and dried at 50° C. in a vacuum oven.

The product can be recrystallized by dissolving in 4 L of EtOAc (50° C.) filtering over supercel, washing with 1 L EtOAc, then charging 3 L of hexane to the 50° C. reaction solution.

The above procedure is shown as follows:



The present invention provides a preferred composition for stabilizing the active ingredient such as, e.g., CI-981 Hemi-Calcium, using basic inorganic pharmaceutically acceptable salts of calcium such as calcium carbonate and calcium hydroxide or basic inorganic pharmaceutically acceptable salts of magnesium such as magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide, or basic inorganic pharmaceutically acceptable salts of lithium such as lithium hydroxide and similar lithium compounds or other similarly suitable alkaline earth metals. The basic inorganic salts of calcium, lithium or magnesium can be utilized in a weight ratio ranging between about 0.1 to 1 and about 50 to 1 of salt compound to active ingredient.

Stabilized solid oral pharmaceutical formulations of the present invention are designed to protect the anti-hypercholesterolemia or anti-hyperlipidemia drug, e.g., CI-981 Hemi-Calcium, of Formula IA (as defined above), from any degrading or processing environment, as well as preserve it from photochemical decomposition during storage. Specifically, the most preferred active chemical ingredient is the compound CI-981 Hemi-Calcium of Formula (IA). The solid formulation according to the present invention also includes, in addition to a stabilizing metal or alkaline earth metal salt, several additives which are known as suitable agents in the art comprising combinations and concentrations as further described below.

The present invention without limiting further provides for diluent additives such as microcrystalline cellulose, hydrous lactose, corn starch, sucrose, silicic anhydride or polysaccharides (as are known as suitable in the art); binders such as methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol or starch; disintegrants such as carboxymethylcellulose calcium, croscarmellose sodium, or starch; and surfactants such as Tween 80 or polyoxyethylene-polyoxypropylene copolymer.

Antioxidants can also be incorporated with the formulations in order to prevent any oxidation of the drug compound. For example, antioxidants that could be used are butylated hydroxyanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid and ascorbic acid.

The most preferred embodiment of the present invention is directed to a solid oral composition including CI-981 Hemi-Calcium as active ingredient, calcium carbonate as the stabilizing component, and other additives.

The basic excipient, calcium carbonate, has been found to provide effective control of the microenvironment of the composition. Further to the present invention, microcrystalline cellulose and hydrous lactose are applied as suitable diluents. In addition, the inventive composition contains a suitable amount of croscarmellose sodium as functional disintegrant. The non-ionic detergent Tween 80 is used as a surfactant. The composition also contains hydroxypropyl cellulose as binder selected from among several applicable substances such as, i.e., polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxymethylcellulose or hydroxypropylmethylcellulose. As anti-oxidants, reagents such as butylated hydroxyanisole, sodium ascorbate, ascorbic acid or others may optionally be incorporated in the composition. Magnesium stearate can be selected from a group including other substances such as stearic acid, palmitic acid, talc or similar lubricating compounds.

Other possible and supplemental ingredients such as preservatives, driers, glidants, or colorants known as conventional by those skilled in the art may be included optionally in the inventive formulation.

In accordance with the preferred embodiment of the present invention, the formulations provide for the following concentration ranges of ingredients by weight: the active ingredient or drug concentration is in the range from about 1% to about 50%; calcium carbonate from about 5% to about 75%; microcrystalline cellulose from about 5% to about 75%; hydrous lactose from about 1% to about 80%; croscarmellose sodium from about 1% to about 15%; hydrox-

ypropylcellulose from about 0.5% to about 6%; Tween 80 from about 0.1% to about 4%; magnesium stearate from about 0.25% to about 2%; and sodium ascorbate [or ascorbic acid] from about 0.0% to about 3%.

The more preferred composition formulated according to the present invention includes the following approximate concentrations of ingredients by weight: 6.91% of the drug; 22% of calcium carbonate; 40% microcrystalline cellulose; 22.19% hydrous lactose; 6% croscarmellose sodium; 2% hydroxypropyl cellulose; 0.4% Tween 80; and 0.5% magnesium stearate; in addition, optionally 0.02% of an antioxidant such as sodium ascorbate.

In particular, CI-981 Hemi-Calcium degrades rapidly in compositions prepared by the wet-granulation method. It has therefore been a surprising discovery that, by adding calcium carbonate, solid formulations for this drug can be prepared by the wet granulation method without compromising the stability of the drug.

Method of Preparation of Pharmaceutical Composition

The method for preparing a solid pharmaceutical composition according to the present invention includes (a) milling an excess of the drug, which can be a compound of Formula I or Formula IA (CI-981 Hemi-Calcium); (b) dissolving at least one binder additive in aqueous surfactant solution; (c) blending the milled drug with at least one drug-stabilizing additive and at least one diluent additive with the drug-stabilizing additive and one half of a disintegrant additive in a rotary mixing vessel equipped with a chopping device; (d) granulating the blended drug ingredient mixture of step (c) with the surfactant/binder solution of step (b) in gradual increments in the chopper equipped mixing vessel; (e) drying the granulated drug mixture overnight at about 50° C.; (f) sieving the dried granulated drug mixture; (g) tumble blending the sieved drug mixture with the remaining amount of the disintegrant additive; (h) mixing separately an aliquot of the drug mixture of step (g) with magnesium stearate, sieving same, and returning same to the drug mixture of step (g) and tumble blending the entire drug mixture; and compressing aliquots of the drug mixture of step (h) into tablet having suitable drug strength.

More particularly, the preferred embodiments of the present invention can be prepared in accordance with the batch procedure given in the examples below.

EXAMPLE 1 (PROTOCOL)

In order to produce 1.5 kg of the composition formulated for peroral therapy, the following steps are taken:

(a) An excess of about 5% by weight of CI-981 Hemi-Calcium is passed through a Model D Fitzmill, which is equipped with a No. O RH screen (0.027"). The mill is run at a high speed with impact forward. Exactly 103.65 g of the milled drug is weighed for step (c).

(b) Tween 80 in an appropriate amount (6.0 g) is dissolved in 100 ml of purified water heated to about 50° C. and mixed for approximately 5 minutes; similarly the hydroxypropyl cellulose (30.0 g) is dispersed in the warm Tween 80 solution and mixed for about 5 minutes; the remaining purified water (500 ml) is added, and the entire mixture is then allowed to hydrate for at least 4 (four) hours.

(c) Thereafter, the milled drug, CI-981 Hemi-Calcium (103.65 g), calcium carbonate (330.0 g), microcrystalline cellulose (600.0 g), hydrous lactose (332.85 g), and 50% of the croscarmellose sodium (45.0 g) are mixed in the 10 liter-Collette Gral for about 5 minutes with the mixer running at 300 rpm and chopper speed 1.

(d) The blended preparation of step (c) is granulated with the solution of step (b) by adding the solution over 30 to 60 seconds with only the mixer running at 300 rpm; then the mixing is continued up to a total of 3 minutes with the mixer speed of 300 rpm and the chopper speed set at 1; the bowl is now lowered and material scraped from the blades and the top of the mixing apparatus. Subsequently, the preparation is remixed for another 3 minutes with the mixer running 300 rpm and the chopper speed setting at 1, with additional amounts of purified water and 3 minutes time increments of mixing, as necessary to obtain adequate granular consistency.

(e) The granulated preparation is spread on paper-lined trays, dried at 50° C. overnight to a loss-only-dose of approximately 2%.

(f) The dried granulation is passed through a Quadromill (Comill) which is equipped with a 0.032" screen.

(g) Approximately half the milled granulation is transferred to a 4 qt. twin shell blender, followed by the remaining 50% (w/w) of the croscarmellose sodium (45.0 g) and finally the remaining milled granulation; the entire mixture is tumble blended for 10 minutes.

(h) Approximately 50 g of the blend resulting from step (g) is removed and mixed with magnesium stearate (7.50 g); this side mixture is passed through a #40 mesh screen and returned to the 4 qt. twin shell blender, and the entire mixture is tumble blended for 5 minutes.

(i) Finally, an appropriate aliquot of the final mixture is compressed to obtain a tablet weight containing the desired drug strength.

EXAMPLE 2

All steps in this Example 2 are the same as in Example 1 except for step (b) which proceeds as follows:

(2b) Firstly, Tween 80 (6.0 g) is dissolved in 100 ml of purified water which has been heated to 50° C.; secondly, after about 5 minutes of mechanical stirring, the hydroxypropyl cellulose (30.0 g) is dispersed in the Tween 80 solution and further mixed for about 5 minutes; thirdly (and optionally) sodium ascorbate (0.3 g) is dissolved in the remaining volume of purified water and added to the Tween 80-hydroxypropyl cellulose mixture. Thereupon the mixture is allowed to hydrate for at least four (4) hours.

EXAMPLE 3

All steps of this alternative embodiment are as described in Example 1 with the exception of process step (b). However, step (b) is as follows:

Firstly, Tween 80 is dissolved in 100 ml of purified water which has been heated to 50° C. Secondly, butylated hydroxyanisole is dissolved in 10 ml of ethanol; which solution is then stirred into the Tween 80 mixture and agitated for 5 minutes. Thirdly, the hydroxypropyl cellulose is dispersed in the above mixture and stirred for approximately 5 minutes. The remaining purified water is added to the mixture which is then allowed to hydrate for at least 4 hours.

The tablets as prepared in all the Examples are film-coated with a film-coating agent known to those of skill in the art to about a 3% weight increase.

The comparative stability of the preferred antihypercholesterolemia or antihyperlipidemia formulations containing CI-981 was tested under highly accelerated stress conditions at elevated temperatures. In particular, the stability of a CI-981 formulation was tested by comparing a powder blend prepared according to the method of Example 3, at 2.5 mg active ingredient dosage in the presence (Ex. 4) or the absence (Ex. 5) of calcium carbonate. The samples were stored in duplicate for two and four weeks at either 45° or 60° C. and then analyzed by reverse phase high performance liquid chromatography ("HPLC"). The HPLC assay procedure employs a Zorbax® Rellance C18 column (8 cm long, 5 micron bead) and a mobile phase of acetonitrile in aqueous buffer (35:65) containing triethylamine, sodium acetate adjusted to pH 4.0. A detection wavelength of 244 nm was used.

The results showed that the calcium carbonate containing preparation of Example 4 incurred no detectable losses of the drug CI-981 after two weeks at 60° C. and only negligible losses of about 0.25% by weight after four weeks at 45° C. and about one half percent by weight at 60° C. In contrast, the formulation of Example 5, lacking calcium carbonate, lost by weight about 2.45% ingredient after four weeks storage at 45° C., about 4.12% of CI-981 after only two weeks and about 5.3% at 60° C. (See Table I).

The second set of comparative data (see Table II) concerns the formulations of Examples 6 and 7 prepared in accord with the protocol of Example 3, wherein the composition was packaged in a capsule at 2.5 mg strength with calcium carbonate (Ex. 6) and without calcium carbonate (Ex. 7). The formulation of Example 6, when measured by HPLC, lost about one half a percent by weight of CI-981 after four weeks at 45° C. and about 2.2% after two weeks at 60° C. The capsule preparation of Example 7 had a CI-981 content which was diminished by about 4.4% after four weeks at 45° C. After two weeks at 60° C., about 14% of CI-981 Hemi-Calcium was lost, as measured by HPLC.

TABLE I

Stability of CI-981 formulations: a powder blend with (Example 4) and without (Example 5) calcium carbonate.

	PERCENT DRUG REMAINING			
	Ex. 4		Ex. 5	
TIME (WEEKS)	45° C.	60° C.	45° C.	60° C.
0	100	100	100	100
2	ND	100	100	95.88
4	99.75	99.48	97.55	94.7

TABLE II

Stability of CI-981 formulations: a capsule with (Example 6) and without (Example 7) calcium carbonate.

	PERCENT DRUG REMAINING			
	Ex. 6		Ex. 7	
TIME (WEEKS)	45° C.	60° C.	45° C.	60° C.
0	100	100	100	100
2	ND	97.81	ND	86
4	99.53	ND	95.6	ND

TABLE III

Stability of CI-981 formulations: a coated tablet with calcium carbonate (Example 8).

	PERCENT DRUG REMAINING	
TIME (WEEKS)	45° C.	60° C.
0	100	100
2	ND	99.11
4	99.47	98.30

ND = not determined

Finally, the stability of the preferred formulation according to the present invention was tested in the form of a coated tablet (Example 8) containing calcium carbonate (see Table III). In particular, the preparation of Example 8 was stored for four weeks at 45° C. and lost about 0.5 by weight of CI-981. After two weeks at 60° C., the composition (Ex. 8) contained about 0.9% less by weight active ingredient and after four weeks at 60° C. about 1.7% less by weight active ingredient. Clearly, the formulation according to the preferred embodiment containing calcium carbonate effectively protects the integrity of the active compounds during both the wet granulation step of the process of preparing the stable solid composition and the subsequent storage in the form of a powder blend, capsule or coated tablet.

Consequently, any variations of the invention described above are not to be regarded as a departure from the spirit and scope of the invention as claimed.

What is claimed is:

1. A pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia characterized by improved stability comprising in a mixture, a compound as active ingredient of structural formula I

wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)$;

R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl, norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with flourine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoylalkoxy of from two to eight carbon atoms;

either R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms; and the other R_2 or R_3 is hydrogen; alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms;

R_4 is alkyl of from one to six carbon atoms, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or trifluoromethyl;

M is a pharmaceutically acceptable metal salt;

at least one stabilizing pharmaceutically acceptable alkaline metal salt additive and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

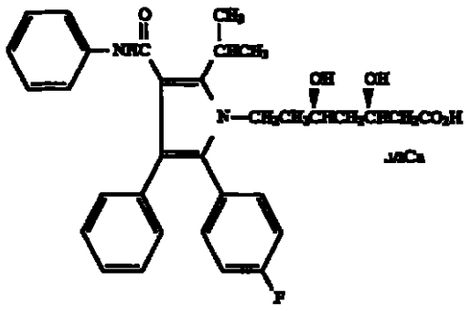
at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one anticoxidant selected from the group consisting of butylated hydroxyanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%.

2. The stable pharmaceutical composition of claim 1 wherein the active ingredient is a pharmaceutically acceptable metal salt of [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid.

3. The stable pharmaceutical composition of claim 2, wherein the pharmaceutically acceptable metal salt is an alkaline earth metal salt.

4. The stable pharmaceutical composition of claim 2, wherein the active ingredient is CI-981 Hemi-Calcium of Formula (IA):



(IA)

and wherein the stabilizing pharmaceutically acceptable metal salt additive is calcium carbonate.

5. The stable pharmaceutical composition of claim 1, 2 or claim 4, wherein the active ingredient dosage is between about 1% and about 50% by weight of the composition.

6. A method for preparing a stable pharmaceutical composition for the peroral treatment of hypercholesterolemia or hyperlipidemia comprising a step of mixing thoroughly about 1% to about 50% by weight of the active ingredient of claim 1, claim 2 or claim 4 with about 5% to about 75% by weight of a stabilizing pharmaceutically acceptable additive.

7. The stable pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable metal salt is an alkaline earth metal salt.

8. The stable pharmaceutical composition of claim 1 wherein the stabilizing pharmaceutically acceptable metal salt additive is an alkaline earth metal salt.

9. The stable pharmaceutical composition of claim 8, wherein the alkaline earth metal salt is selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate and aluminum magnesium hydroxide.

10. The stable pharmaceutical composition of claim 1, wherein the stabilizing pharmaceutically acceptable metal salt additive is calcium carbonate.

11. The stable pharmaceutical composition of claim 10 wherein the stabilizer calcium carbonate is in the range from about 5% to about 75% by weight of the composition.

12. The stable pharmaceutical composition of claim 1, further comprising an antioxidant.

13. The stable pharmaceutical composition of claim 12 wherein the composition comprises by weight between about 5% and about 75% microcrystalline cellulose; between about 1% and about 80% of hydrous lactose; between about 1% and about 15% of croscarmellose sodium; between about 0.5% and about 6% hydroxypropyl cellulose; between about 0.1% and about 4% of Tween 80; between about 0.25% and about 2% of magnesium stearate; and up to about 3% of sodium ascorbate or butylated hydroxyanisole of the total solid composition.

14. A stabilized solid pharmaceutical composition for peroral treatment of hypercholesterolemia or hyperlipidemia comprising in solid unit dosage form an active ingredient [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt and a stabilizer selected from the group consisting of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

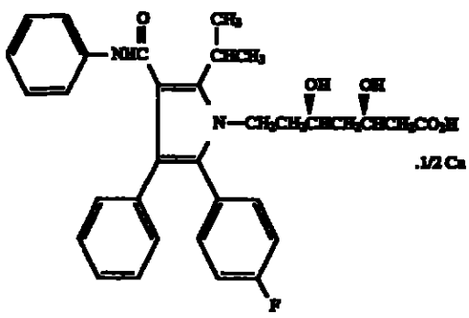
at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one anticoxidant selected from the group consisting of butylated hydroxyanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%.

15. A method for preparing a stabilized pharmaceutical composition formulated for peroral therapy of hypercholesterolemia or hyperlipidemia comprising:

(a) milling an excess of the drug, CI-981 Hemi-Calcium of the formula IA:



(b) dissolving at least one binder additive in aqueous surfactant solution;

(c) blending the milled drug with at least one drug-stabilizing alkaline earth metal salt additive and at least one diluent additive ingredient with the drug-stabilizing additive and one half of a disintegrant additive in a rotary mixing vessel equipped with a chopping device;

(d) granulating the blended drug mixture of step (c) with the surfactant/binder solution of step (b) in gradual increments in the chopper equipped mixing vessel;

(e) drying the granulated drug mixture overnight at about 50° C.;

(f) sieving the dried granulated drug mixture;

(g) tumble blending the sieved drug mixture with the remaining amount of the disintegrant additive;

(h) mixing separately an aliquot of the step (g) drug mixture with magnesium stearate, sieving same, and returning same to the drug mixture of step (g) and tumble blending the entire drug mixture; and compressing aliquots of the step (h) drug mixture into tablets.

16. The method claimed in claim 15, wherein in step (c) the drug stabilizing additive comprises a basic inorganic salt of calcium or magnesium.

17. The method claimed in claim 15, wherein in step (b) the binder additive comprises methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol or starch; and the surfactant comprises Tween 80 or polyoxyethylene-polyoxypropylene copolymer.

18. The method of claim 15 wherein in step (c) the disintegrant additive comprises croscarmellose sodium, carboxymethyl cellulose calcium or starch.

19. The method claimed in claim 15 wherein in step (c) the diluent additive is selected from the group consisting of microcrystalline cellulose, hydrous lactose, corn starch, sucrose, silicic anhydride and mixtures thereof.

20. The method claimed in claim 15 wherein the diluent additive is at least one polysaccharide.

21. A peroral pharmaceutical composition for treating hypercholesterolemia comprising an effective, cholesterol synthesis inhibitory amount of the enantiomer [R-R*,R*)]-2(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, hemicalcium salt; stabilized by calcium carbonate, and comprising by weight of the total solid composition at least one binder selected from the group consisting of methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxymethylpropylcellulose, polyvinylpyrrolidone, polyvinylalcohol, starch, and hydroxymethylcellulose comprising by weight between about 0.5% and about 6%;

at least one diluent selected from the group consisting of microcrystalline cellulose, hydrous lactose, cornstarch, sucrose, and silicic anhydride comprising by weight between about 1% and about 80%;

at least one disintegrant selected from the group consisting of carboxymethylcellulose, croscarmellose and starch comprising by weight between about 1% and about 15%;

at least one surfactant selected from the group consisting of polyoxyethylene sorbitan and polyoxyethylene-polyoxypropylene copolymer comprising by weight between about 0.1% and about 4%;

at least one lubricant selected from the group consisting of magnesium stearate, stearic acid, palmitic acid, and talc comprising by weight between about 0.25% and about 2%;

and optionally at least one antioxidant selected from the group consisting of butylated hydroxyanisole, sodium ascorbate, butylated hydroxytoluene, sodium metabisulfate, malic acid, citric acid, and ascorbic acid comprising by weight up to about 3%, in a dosage of solid enantiomer ranging from about 0.1 to about 8.0 mg/kg body weight per day.

22. A method of treating hypercholesterolemia or hyperlipidemia comprising a therapeutically effective unit dosage of the peroral pharmaceutical composition of claim 21 in the form of tablets or capsules.

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