

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

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

②

Número del expediente: 05-124741

Solicitante: WARNER-LAMBERT COMPANY LLC.

SOLICITUD
PUBLICADA

Apoderado: CARLOS REINALDO OLARTE GARCIA.

Título de la nueva creación o denominación del signo: "COMPOSICIONES
ESTABLES DE ATORVASTATINA PREPARADAS CON GRANULACIÓN EN HÚMEDO."

Gaceta: 565

③

OPOSICIÓN PRESENTADA POR:

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

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. _____

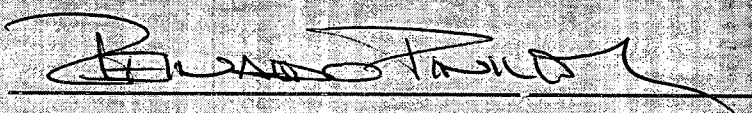
Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: REINALDO PINILLA MORENO

FIRMA: 

C.C. 80425609

TP. 91563 CSJ

PRESENTACION PERSONAL

27 SET 2006

En Bogotá, D.C. a _____ se present. _____

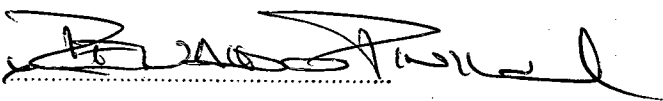
en la Notaría Décima, cuya titular es SERGIO FRANCO LEON

Reinaldo Pinilla Moreno

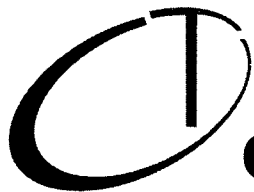
Con cédula No. 80425609 TP. 91563

Expedida en Usaquén y dijo _____ que

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

letra. En constancia se firma 





Optimum

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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 124741

Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIONES ESTABLES DE ATORVASTATINA
PREPARADAS CON GRANULACIÓN EN HÚMEDO".

Solicitante : WARNER LAMBERT COMPANY LLC.

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 565 del 30 de Junio 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 ESTABLES DE ATORVASTATINA PREPARADAS CON GRANULACIÓN EN HÚMEDO**", solicitada por **WARNER LAMBERT COMPANY LLC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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DE
GIO

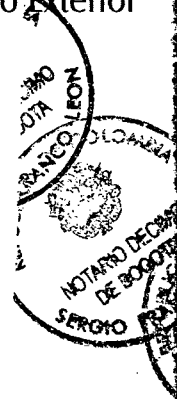
1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular una estatina. 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 9 de diciembre de 2005, reivindicando prioridad bajo la solicitud US20030478119P del 2003-06-12 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 565 del 30 de junio de 2006, página 500, N° publicación 230, cuya publicación internacional corresponde a la WO04/110431 del 23-12-2004.

2.2. La solicitud colombiana 05 124.741 objeto de la presente oposición, se refiere a una composición farmacéutica de atorvastatina granulada en húmedo con menos de aproximadamente 5 por ciento en peso de un aditivo constituido por una sal de

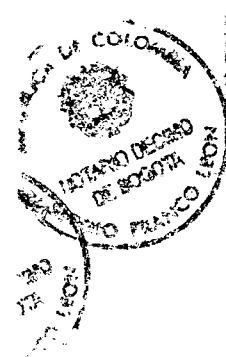
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metal alcalino- térreo, que comprende: (a) atorvastatina, en donde dicha atorvastatina es al menos algo desordenada o una mezcla de las formas desordenada y cristalina de atorvastatina o una de sus sales farmacéuticamente aceptables; y (b) un desintegrante o una combinación de desintegrantes, en donde dicha composición farmacéutica de granulada en húmedo, contiene no más de aproximadamente 3% de lactona de atorvastatina basado en la relación del área del pico de lactona comparada con las áreas integradas de todos los picos relacionados con el fármaco empleando HPLC; en donde dicha composición incluye menos de aproximadamente 0,5% en peso de Tween 80; en donde dicha forma de dosificación unitaria es un comprimido o una cápsula; en donde dicho desintegrante o combinación de desintegrantes está presente en una proporción entre aproximadamente 1 y 10% (en peso/peso) de dicha composición. Igualmente, la solicitud se refiere a un método de preparación, a un método de tratamiento y a un Kit.

2.3. En primera instancia, se debe advertir que la reivindicación 13 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



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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, 2002-09-19.
- D2: WO0176566, 2001-10-18.

2.5. Ahora bien, el documento D1, particularmente en la descripción, tablas 1 y 4 así como los ejemplos 1 a 6, se refiere a composiciones preparadas por granulación en húmedo, conteniendo una sal de adición de un metal térreo no alcalino y comprendiendo atorvastatina amorfa, hidroxipropilcelulosa y cerca de 0,5% de Tween 80. Estas composiciones reveladas en el documento D1, por lo tanto conforman una igual composición farmacéutica de atorvastatina granulada en húmedo constituido por una sal de metal alcalino- térreo. Así las cosas, es claro que este documento D1, revela una misma propuesta como solución que incluye una composición que comprende atorvastatina como ingrediente activo 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 en la descripción y reivindicaciones, particularmente en el ejemplo 8 a una composición farmacéutica útil para la administración a mamíferos contenido atorvastatina, crospovidona, lactosa monohidrato y povidona, la cual según dicho documento D2, fue premezclada y granulada usando una solución de alcohol de polisorbato 80. Según dicho documento anterior D2, el peso aproximado para una pastilla que contiene 10 mg de atorvastatina es de cerca de 150 mg. Por lo tanto a la luz de la combinación de

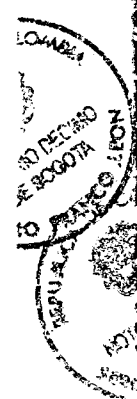
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los documentos D2 con lo expuesto en el documento D1, la solicitud carece de altura o nivel inventivo.

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 contenedor 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 contenedor 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 05 124.741 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 preparada con granulación en húmedo 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 preparada con granulación en húmedo 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 presente oposición y negar el registro Patente de invención denominada ***"COMPOSICIONES ESTABLES DE ATORVASTATINA PREPARADAS CON GRANULACIÓN EN HÚMEDO"***, solicitada por **WARNER LAMBERT COMPANY LLC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 565.

3. PRUEBAS

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

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- D1: WO02072073, 2002-09-19.
- D2: WO0176566, 2001-10-18.

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, 2002-09-19.
- D2: WO0176566, 2001-10-18.

6. NOTIFICACIONES

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

DE COLOMBIA
NOTARIO DE BOGOTÁ
SERGIO
DE COLOMBIA
NOTARIO DE BOGOTÁ
SERGIO
BOGOTÁ
RANCO LEON

Señor Superintendente,


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 27 SET 2006 se present. 0

en la Notaria Décima, cuya titular es SERGIO FRANCO LEON
REINALDO PINILLA MORENO

Con cédula No. 80425609-10-91563

Expedida en Colombia y dijo que
el anterior documento es cierto y que la firma es de su puño y

letra. En constancia se firma 



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JTA
FRANCO LEON

WABA



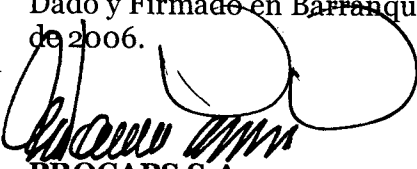
PODER ESPECIAL

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. **05-124.741**, titulada **COMPOSICIONES ESTABLES DE ATORVASTATINA PREPARADAS CON GRANULACIÓN EN HÚMEDO** de **WARNER LAMBERT COMPANY LLC**, publicada en la gaceta No. 565 del 30 de Junio de 2006.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 18 días del mes de Septiembre de 2006.

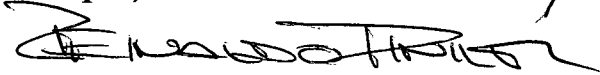

PROCAPS S.A.

WALTER TANAKA TATEKAWA

C.C. N° 16.251.923 de Palmira

Representante Legal - *afco*

Acepto,



REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

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

SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que este escrito fue
presentado Personalmente por WALTER
TORRES TOTEKANA

Identificado con: 26251.923

Expedida en: 22 SET 2006

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

Firma

Huella del Compareciente

22 SET 2006

REPUBLICA DE COLOMBIA

NOTARIA SEGUNDA

ADY ISABEL NAMEN SEGURA

NOTARIA

CIRCULO DE BARRANQUILLA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
 Rad: 05-124741- -00002-0000
 Fec: 2006-09-27 16:01:11 Dep. 2020 NUECREACIONES.
 Tm. 11 PATENTEIVII
 Eve: 379 FASENACIONALII
 Act 400 OPOSIOBSERVTER Folios: 74

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 66,667
 FECHA : AGOSTO 30 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
SYNCPHARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	47264305	27/01/2006	11,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	11,000.00
		TOTAL :	\$ 11,000.00

SON: ONCE 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.

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-124741- -00002-0000
Fec: 2006-09-27 16:01:11 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIVII
Eve: 379 FASENACIONALII
Act 400 OPOSIOBSERVTER Folio 6: 74

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

IFICACION DE EXCEDENTE : 06 - 74,812
FECHA : SEPTIEMBRE 27 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OTEC LTDA.	CONSIGNACION	BANCO POPULAR	050-00110-6	53372192	27/09/2006	235,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS
			TOTAL : \$ 235,000.00

SON: DOSCIENTOS TREINTA Y CINCO 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.

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***** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
11*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No. 1.190 del 22 de Julio de 1976, otorgada 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, otorgada 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, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12.705 del libro respectivo, la sociedad antes mencionada----- se transformo en sociedad de responsabilidad limitada bajo al razon social 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, otorgada 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, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67.218 del libro respectivo, la sociedad antes mencionada-----

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

C E R T I F I C A

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

C E R T I F I C A

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



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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 fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e) La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, com-

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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 gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A

CAPITAL	Nro Acciones	Valor 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 correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir 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 doscientos cincuenta mil dolares de los

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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 o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la 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 interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el 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, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar

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la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. -----

C E R T I F I C A

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

C E R T I F I C A

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

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

C E R T I F I C A

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

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

C E R T I F I C A

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

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

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio,

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

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

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, 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 confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes 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 suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (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 DIAZ GRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y 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 conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion 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 Exterior y/o 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 sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a

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suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarías y demás 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 según documento privado del 22 de Febrero de 2005, inscrito en esta Cámara 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 actúa como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representación de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los trámites o registros de comercio exterior ante la dirección de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de información de las autoridades aduaneras en los órdenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Pública No.1.613 del 28 de Junio del 2.005, otorgada en la Notaría Segunda de Barranquilla, inscrita en esta Cámara 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 condición de Presidente y Representante Legal de la sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a los siguientes señores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800.000), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. GRUPO A: MIRIAM RODRIGUEZ DIAZ, C.C.No. 41.473.569. GRUPO B: NELSON SUAREZ CHAVEZ, C.C.No.79.417.971.-----.

C E R T I F I C A

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

C E R T I F I C A

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

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

03-08029695 024802 PROCAPS S.A.
Barranquilla, 18 de Sep/bre de 2006

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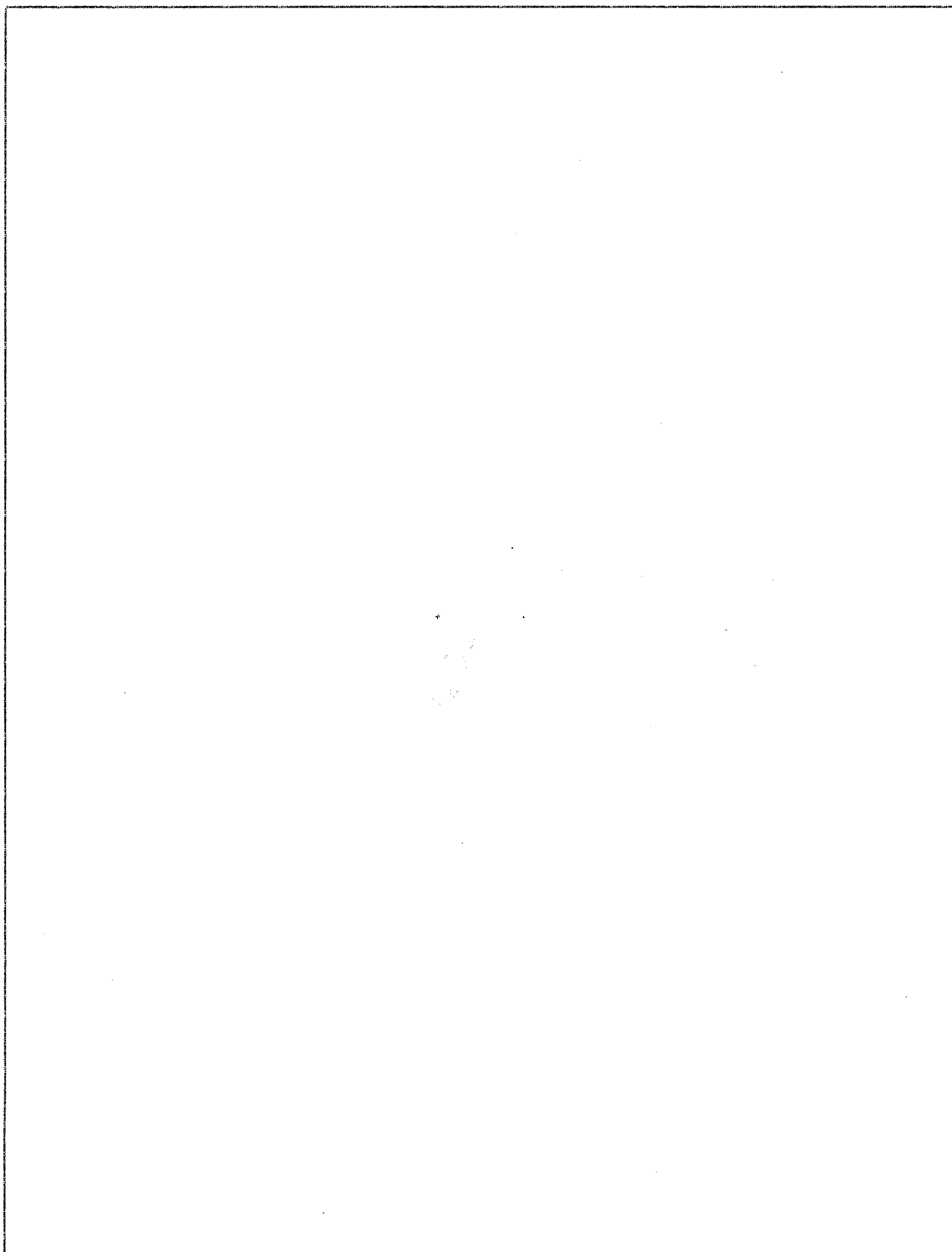
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

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ANEXO 1



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

(57) Abstract: Atorvastatin calcium, the substance known by the chemical name (R-(R*,R*))-(4-fluorophenyl)- β , δ -dihy-
droxy-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.

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

The present invention relates to atorvastatin calcium in a
5 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
10 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)-
15 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;
20 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
25 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
30 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

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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 atorvastatin 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

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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 alkalisng or a buffering substance which improves the bioavailability of atorvastatin by increasing its solubility and dissolution rate in aqueous solutions.

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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 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

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solutions is markedly improved at pH values equal to or greater than pK_a+1 whereas surprisingly differences between atorvastatin calcium in crystal or amorphous form appear to be negligible. The pK_a 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 pK_a+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

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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.

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Table 1

Composition	A1	A2	A3	A4
Atorvastatin amorphous, micronized*	20.00	20.00	20.00	20.00
Microcrystalline 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 ₂ HPO 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

- 5 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

- 10 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 ₃ PO 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 compositions 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 pK_a+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.

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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

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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 alkalisng 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 alkalisng or buffering substance, a disintegrating agent and if required a surfactant and other conventional

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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.

- 5 • 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
- 10 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,
- 15 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,
- 20 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.
- 25 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 Na₂HPO₄

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 ₂ HPO 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 Na₃PO₄, respectively

- 5 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 ₃ PO ₄	-	80.0	-	80.0
Demi water for granulation	80.0	80.0	80.0	80.0

- 10 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

- 15 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:

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	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)

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155Claims:

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.
- 5 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.
- 10 4. The composition according to claim 3 wherein the pH adjusting substance increases the pH of an aqueous solution equal to or greater 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.
- 15 6. The composition according to any of the claims 2 to 5, wherein the pH adjusting substance is at least one substance selected from alkalis and buffering substances.
7. A pharmaceutical formulation comprising atorvastatin calcium as active ingredient,
- 20 **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,
25 wherein the atorvastatin calcium is present in the formulation in different physical forms.

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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
5 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,
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
15 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.
- 20 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
25 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.
- 5 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 Na₃PO₄ and Na₂HPO₄, and
10 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
15 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
20 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
25 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
30 administrable form.

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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
5 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
- 10 (g) further processing including tritulating 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:

- 15 (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
20 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
25 the pH of the acidic environment to a pH equal to or greater than pK_a+1 of atorvastatin calcium.

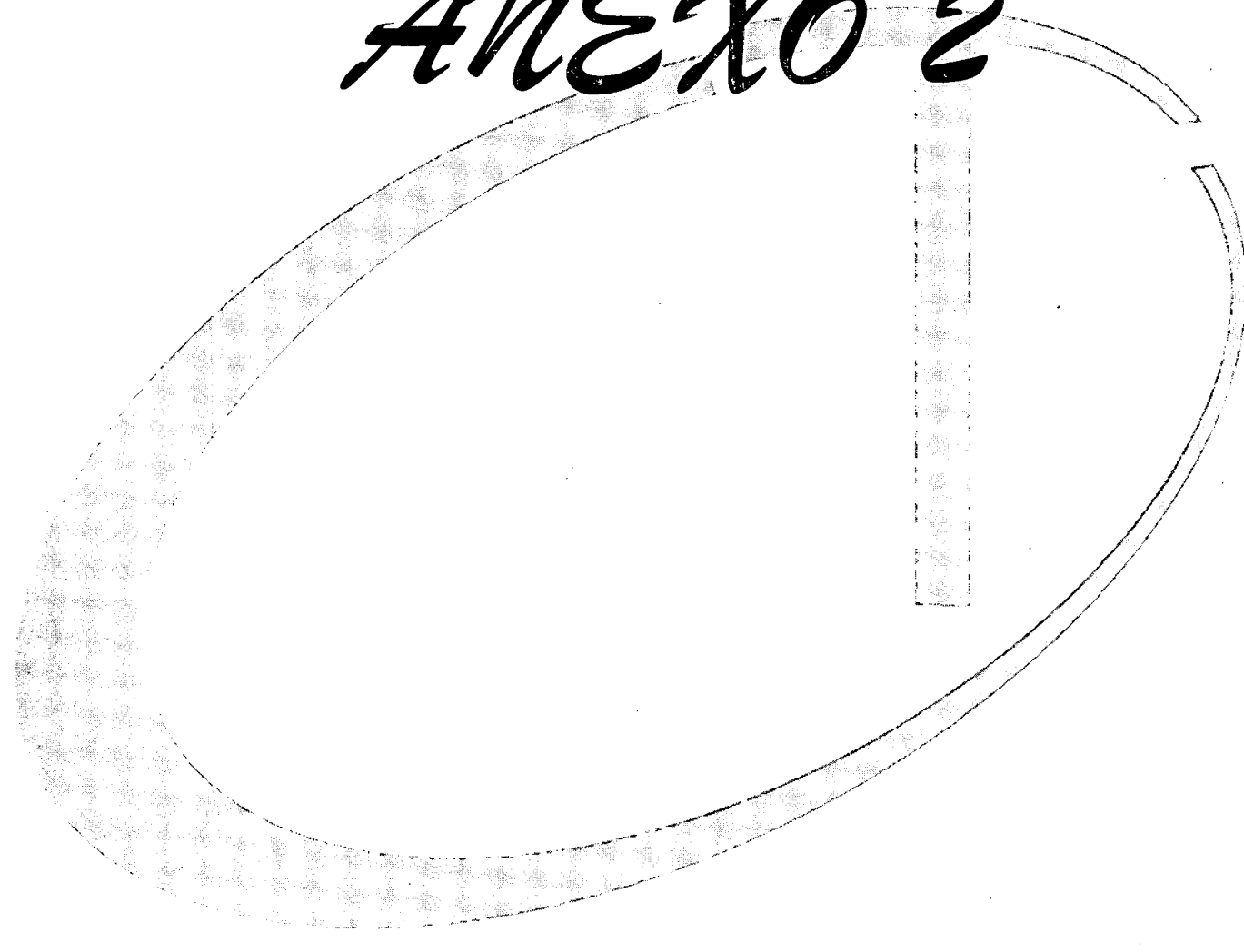
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28. The process according to claim 27, wherein the addition of the pH adjusting substance is adjusted such that a single administration of the formulation increases the pH of the acidic environment to a pH of 5.5 or more.

5 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
10 any of the claims 21 to 29 for the treatment of hypercholesterolemia and hyperlipidemia.

ANEXO 2



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(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS CONTAINING 7-SUBSTITUTED-3,5-DIHYDROXYHEPTANOIC ACIDS OR 7-SUBSTITUTED-3,5-DIHYDROXYHEPTENOIC ACIDS

(57) Abstract: Pharmaceutical compositions that have excellent storage stability even though they include an active component that is susceptible to degradation in an acidic environment are disclosed. The stabilized pharmaceutical composition of the invention includes a ring-opened 7-substituted-3,5-dihydroxyheptanoic or a ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or a pharmaceutically acceptable salt thereof, as an active component and a stabilizing effective amount of at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or combination thereof; wherein the stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer of a combination of other stabilizers. The pharmaceutical composition may optionally include one or more pharmaceutically acceptable excipients such as a filler, a disintegrating agent and one or more lubricants such as magnesium stearate to aid compression where a tablet dosage form is desired.

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**STABLE PHARMACEUTICAL COMPOSITIONS CONTAINING
7-SUBSTITUTED-3,5-DIHYDROXYHEPTANOIC ACIDS OR 7-SUBSTITUTED-
3,5-DIHYDROXYHEPTENOIC ACIDS**

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CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional application Serial No. 60/195,916, filed April 10, 2000, which is incorporated entirely herein by reference.

10

FIELD OF THE INVENTION

The present invention relates to stabilized pharmaceutical compositions comprising statins, and more particularly to stabilized pharmaceutical compositions containing ring-opened 7-substituted-3,5-dihydroxyheptanoic acids or ring-opened 7-substituted-3,5-dihydroxyheptenoic acids, or pharmaceutically acceptable salts thereof. The present invention also relates to the use of such stabilized pharmaceutical compositions for the treatment of dyslipidemias including hyperlipidemia, hypercholesterolemia and hypertriglyceridemia.

20

BACKGROUND OF THE INVENTION

Complications of cardiovascular disease, such as myocardial infarction, stroke, and peripheral vascular disease account for about half of the deaths in the United States. A high level of low density lipoprotein (LDL) in the bloodstream has been linked to the formation of coronary lesions that obstruct the flow of blood and can rupture and promote thrombosis. Goodman and Gilman, *The Pharmacological Basis of Therapeutics* 879 (9th ed. 1996). Reducing plasma LDL levels has been shown to reduce the risk of clinical events in patients with cardiovascular disease and in patients who are free of cardiovascular disease but who have hypercholesterolemia. Scandinavian Simvastatin Survival Study Group, 1994; Lipid Research Clinics Program, 1984a, 1984b. In addition, low levels of high density lipoprotein (HDL) and high levels of triglycerides (TG) are also

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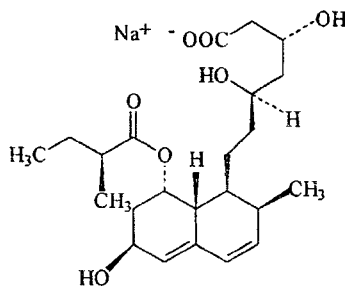
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known to be associated with increased incidence of cardiovascular disease and primary and secondary coronary events including, but not limited to, myocardial infarction.

Statins are currently among the most therapeutically effective drugs available for reducing the level of LDL in the blood stream of a patient at risk for cardiovascular disease. Statins are also known to raise HDL cholesterol levels and decrease total triglyceride levels. Specific examples of statins include, *inter alia*, compactin, lovastatin, mevastatin, simvastatin, pravastatin, atorvastatin, cerivastatin, itavastatin and fluvastatin. The mechanism of action of statins has been elucidated in some detail. It is believed that statins disrupt the biosynthesis of cholesterol and other sterols in the liver by competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase enzyme ("HMG-CoA reductase"). HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, which is the rate determining step in the biosynthesis of cholesterol. Consequently, its inhibition leads to a reduction in the rate of formation of cholesterol in the liver.

Pravastatin is the common name of the chemical compound [1S-[1 α (β S*, δ S*)2 α ,6 α ,8 β (R*),8 α]]-1,2,6,7,8,8a-hexahydro- β , δ ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthaleneheptanoic acid monosodium salt, disclosed in U.S. Patent No. 4,346,227 to Terahara et al.

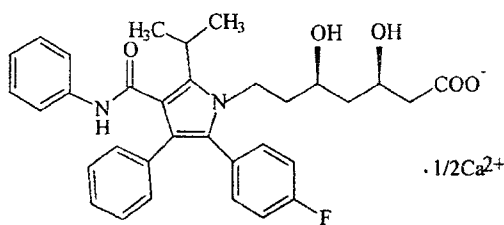
Pharmaceutical compositions that include a medicament that is unstable in an acidic environment have been thought to require a basic excipient to enhance storage stability. For example, pravastatin sodium is an HMG-CoA reductase inhibitor having the structural formula:



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Pravastatin sodium (sold in the U.S. under the trademark **PRAVACHOL®**) is sensitive to a low pH environment and will degrade to form its lactone and various isomers. Joshi et al. stated in U.S. Patent No. 5,180,589 that it is necessary to add one or more basifying agents to impart a desired pH of at least 9 to an aqueous dispersion of a pravastatin composition in order to stabilize it. Among the basifying agents disclosed in U.S. Patent No. 5,180,589 are magnesium oxide, aluminum oxide, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide or lithium hydroxide and alkaline earth metal hydroxides such as calcium hydroxide or magnesium hydroxide. Magnesium oxide is said to be the preferred basifying agent. Thus, the types of basifying agents disclosed in U.S. Patent No. 5,180,589 as stabilizing agents are inorganic metal oxides and hydroxides, which are generally considered to be strongly alkaline agents.

Atorvastatin calcium, another HMG-CoA reductase inhibitor, is described in U.S. Patent No. 5,273,995 to Roth. Atorvastatin calcium is [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 has the following structural formula:



Atorvastatin calcium (sold in the U.S. under the trademark **LIPITOR®**) is susceptible to a low pH environment and can degrade to the corresponding lactone in an acidic environment. Mills et al. have stated in U.S. Patent No. 5,686,104 that this and similar compounds in an oral pharmaceutical formulation for the treatment of

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hypercholesterolemia or hyperlipidemia are stabilized by combination with at least one basic inorganic pharmaceutically acceptable calcium, magnesium, aluminum or lithium salt. Examples of these salts are calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum magnesium hydroxide or lithium hydroxide. Calcium hydroxide is disclosed as the preferred alkaline earth stabilizing agent. Thus, as in U.S. Patent No. 5,180,559, the stabilizing agents disclosed in U.S. Patent No. 5,686,104 are basic inorganic pharmaceutically acceptable salts.

WO 00/35425 discloses the stabilization of an HMG-CoA reductase inhibitor in a solid formulation with a buffering agent. Among the buffering agents disclosed in WO 00/35425 are sodium or potassium citrate, sodium phosphate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulphate, sodium or magnesium carbonate, sodium ascorbate, benzoate, sodium or potassium hydrogen carbonate, lauryl sulphate, or mixtures of such buffering agents. Among the HMG-CoA reductase inhibitors disclosed in WO 00/34525 are atorvastatin, pravastatin, fluvastatin and cerivastatin, which are said to be particularly sensitive to an acidic environment in which hydroxy acids are degraded into the corresponding lactone.

As used herein, the term "dyslipidemia" refers to an abnormal level of one or more of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein B (Apo B), apolipoprotein A (Apo A), very low density lipoprotein cholesterol (VLDL-C), and intermediate density lipoprotein cholesterol (IDL-C). By "abnormal" is meant a level generally accepted by the relevant medical community as an undesirable level, which may be higher or lower than desirable, and which may be beneficially adjusted by treatment of a patient with a stabilized statin composition as disclosed herein. Guidelines for the detection, evaluation and treatment of dyslipidemias are promulgated by the National Institute of Health's National Cholesterol Education Program ("NCEP"). The NCEP guidelines suggest when treatment with therapeutic agents such as the statin compounds disclosed herein, are indicated for the treatment of a dyslipidemia such as

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hypercholesterolemia. Initiation of treatment with a statin compound, in accordance with the NCEP guidelines depends on numerous factors. Among such factors are included abnormal levels of one or more of Total-C, LDL-D, TG, Apo B, Apo A, VLDL-C and IDL-C; familial history of cardiovascular disease or event; prior cardiovascular disease; and, prior occurrence of an acute cardiovascular event, such as myocardial infarction, etc.

By "therapeutically effective amount" as used herein is meant an amount of active component in the stabilized pharmaceutical compositions of the present invention which is effective to beneficially treat a dyslipidemia.

The term "dyslipidemia" thus encompasses "hyperlipidemia", "hypercholesterolemia" and "hypertriglyceridemia" which terms as used herein refer to abnormally high levels of one or more of Total-C, LDL-C, TG, Apo B, VLDL-C and IDL-C. Thus, the term "dyslipidemia" includes all of the dyslipidemias classified by the Frederickson Classification System, including Frederickson Type I hyperlipidemia, Frederickson Types IIa and IIb primary hypercholesterolemia, Frederickson Type IV hypertriglyceridemia, Frederickson Type III dysbetalipoproteinemia, and Frederickson Type V hyperlipidemia.

By "stabilized pharmaceutical composition" as used herein is meant that after storage for six months at 40°C and 75% relative humidity, no more than about 10%, preferably no more than about 5%, and more preferably, no more than about 1% by weight of the active component initially present in the composition degrades into the corresponding lactone.

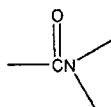
By "stabilizing effective amount" as used herein is meant an amount by weight of a stabilizing compound present in the pharmaceutical composition which is effective to provide a stabilized pharmaceutical composition.

By "stabilizing effective amount of another stabilizer or a combination of other stabilizers" as used herein is meant an amount of a stabilizing compound or

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combination of stabilizing compounds, other than the amido-group containing polymeric stabilizing compound or compounds as used in the pharmaceutical compositions of the subject invention, which would provide a stabilized pharmaceutical composition as defined herein. Thus, the present invention is not meant to be construed as excluding compounds that may provide some stabilizing effect, but only to exclude a stabilizing effective amount of one or more of such compounds. As disclosed hereinabove, other such stabilizing compounds include, for example, inorganic alkaline and alkaline earth metal salts, oxides and hydroxides as disclosed, for example, in U.S. Patent No. 5,180,589; U.S. Patent No. 5,686,104, and buffering agents as disclosed, for example, in WO 00/34525.

By "amido-group containing polymeric compound" as used herein is meant a pharmaceutically acceptable polymeric compound containing, either in a pendant group attached to the polymer backbone, or as a component of the polymer backbone, an amido group, i.e., a group having the formula:



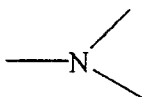
wherein the carbon atom is bonded to another atom and the nitrogen atom is bonded to two other atoms. The term "amido-group containing polymeric compound" is meant to include combinations of different amido-group containing polymeric compounds. Preferred amido-group containing polymeric compounds are those in which nitrogen and carbon are covalently bonded to atoms other than hydrogen. By "tertiary amide group" as used herein is meant an amido-group in which nitrogen is covalently bonded, not including its bond to the carbonyl group, to two atoms neither of which is hydrogen.

By "amino-group containing polymeric compound" as used herein is meant a pharmaceutically acceptable polymeric compound containing, either in a pendant group

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attached to the polymer backbone, or as a component of the polymer backbone, an amino group, i.e., a group having the formula:

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10 wherein the nitrogen atom is bonded to three other atoms. The term "amino-group containing polymeric compound" is meant to include combinations of different amino-group containing polymeric compounds." Preferred amino-group containing polymeric compounds are those in which the nitrogen atom is covalently bonded to atoms other than hydrogen. Particularly preferred amino-group containing polymeric compounds are those
15 in which the amino group is quaternized, in which case, the amino-group containing polymeric compounds can be equivalently described as a quaternary ammonium salt group containing polymeric compound. The agent used to quaternize the amino group is not critical. Methyl chloride is a preferred quaternizing agent, however, any chemical reagent which is pharmaceutically acceptable and which forms a quaternary ammonium salt by
20 reaction with a tertiary amino group may be used. As examples of quaternizing agents may be mentioned, without limitation, C₁-C₃ straight or branched chain alkyl halides, phosphates, carbonates, or sulfates; C₇-C₁₀ aralkyl halides, phosphates or sulfates, and mixtures thereof. Examples of preferred quaternizing agents include but are not limited to methyl chloride, benzyl chloride, diethyl sulfate, dimethyl carbonate, trimethyl phosphate,
25 dimethyl sulfate or mixtures thereof. By "tertiary amino group" as used herein is meant an amino group in which nitrogen is covalently bonded three atoms none of which are hydrogen.

30 By "aqueous dispersion" as used herein in reference to measurement of the pH of the stabilized pharmaceutical compositions of the present invention is meant an amount of a stabilized pharmaceutical composition of the present invention disintegrated

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in an amount of deionized water sufficient to provide a concentration of active component of about 1 mg/ml

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SUMMARY OF THE INVENTION

10 In one aspect, the present invention is directed to a stabilized pharmaceutical composition for the treatment of dyslipidemia, comprising, as an active component, at least one ring-opened 7-substituted-3,5-dihydroxyheptanoic acid or ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or a pharmaceutically acceptable acid salt thereof, and a stabilizing effective amount of at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or
15 combination thereof; wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers.

20 In another aspect, the present invention is directed to a method for the treatment of dyslipidemia, comprising the step of orally administering to a patient in need of such treatment a therapeutically effective unit dosage of a stabilized pharmaceutical composition comprising, as an active component, at least one ring-opened 7-substituted-3,5-dihydroxyheptanoic acid or ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or a pharmaceutically acceptable acid salt thereof, and a stabilizing effective amount of at least one amido-group containing polymeric compound or at least one amino-group
25 containing polymeric compound, or combination thereof; wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers..

30

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that a stabilized pharmaceutical composition, especially one for the treatment of dyslipidemia, comprising at least one ring-opened 7-substituted-3,5-dihydroxyheptanoic acid or ring-opened 7-substituted-3,5-dihydroxyheptenoic acid or a pharmaceutically acceptable salt thereof, can be made by providing, in the pharmaceutical composition, a stabilizing effective amount of at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or combination thereof; wherein the stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers. Accordingly, in a preferred embodiment, the present invention provides a stabilized solid pharmaceutical formulation for oral administration comprising a ring-opened 7-substituted-3,5-dihydroxy-heptanoic acid such as pravastatin or atorvastatin or a ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or a pharmaceutically acceptable salt thereof, that is a HMG-CoA reductase inhibitor, as an active ingredient, and a stabilizing effective amount of at least one amido-group containing polymeric compound or a stabilizing effective amount of at least one amino-group containing polymeric compound, or combination thereof; wherein the stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers.

The invention is particularly adapted to solid pharmaceutical compositions containing pravastatin or atorvastatin, or a pharmaceutically acceptable salt thereof, as the active component of the composition. Among the most preferred active components are pravastatin sodium and atorvastatin calcium. Pravastatin sodium and atorvastatin calcium are ring-opened 7-substituted-3,5-dihydroxy-heptanoic acids. However, it is to be understood that the pharmaceutical compositions of the subject invention may contain any ring-opened 7-substituted-3,5-dihydroxy-heptanoic acid. Thus, the pharmaceutical compositions of the subject invention may also contain, as an active ingredient, a statin such as compactin (mevastatin), lovastatin, or simvastatin in the ring-opened form; or a pharmaceutically acceptable salt thereof. Therefore, the pharmaceutical composition of

the subject invention can include, as an active ingredient, a crystalline salt of simvastatin as disclosed, for example, in EP 1036783A1, the disclosure of which is entirely incorporated herein by reference.

5 The stabilized pharmaceutical composition of the subject invention can also include as an active ingredient, a ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or a pharmaceutically acceptable salt thereof. Examples of these active ingredients include, but are not limited to the HMG-CoA reductase inhibitors fluvastatin, cerivastatin and itavastatin; or a pharmaceutically acceptable salt thereof.

10 The ring-opened 7-substituted-3,5-dihydroxy-heptanoic acid or 7-substituted-3,5-dihydroxyheptenoic acid can be used in the stabilized pharmaceutical compositions of the present invention either as the free acid or as any pharmaceutically acceptable salt thereof. The free acid can be prepared, for example, by hydrolysis of the
15 corresponding lactone form or by treatment of the salt form of the acid with cationic exchange resin and evaporating the water portion. The free acid can be used to form the pharmaceutically acceptable salt form, by conventional methods known in the art. Among preferred pharmaceutically acceptable salts are metal and amine salts. The term
20 "pharmaceutically acceptable metal salt" thus includes, but is not limited to, sodium, potassium, lithium, calcium, magnesium, aluminum, iron, or zinc salts. Such salts may be 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, and ammonium hydroxide. The term "pharmaceutically acceptable amine salt" includes, but is not limited to, salts
25 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.

30 The amount of the active ingredient in the stabilized pharmaceutical compositions of the present invention will be a therapeutically effective amount. A therapeutically effective amount will generally be an amount within the range of from about 0.05 to about 70%, and preferably an amount within the range of from about 1 to

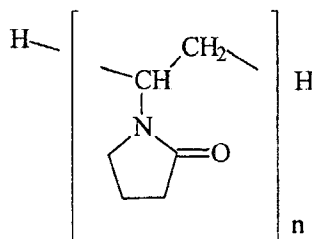
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about 60% by weight of the composition. It is understood that higher or lower weight percentages of the active ingredient may be present in the pharmaceutical compositions.

Also present in the stabilized pharmaceutical compositions of the present invention is a stabilizing effective amount of at least one amido-group containing polymeric compound or a stabilizing effective amount of at least one amino-group containing polymeric compound, or a stabilizing effective amount of a combination of at least one amido-group and at least one amino-group containing polymeric compound.

An amido-group containing polymeric compound is any pharmaceutically acceptable polymeric compound having, either in a pendant group attached to the polymer backbone, or as a component of the polymer backbone, an amido group as defined hereinabove.

Preferred examples of the amido-group containing polymeric compound include, but are not limited to, polyvinylpyrrolidone (PVP), which is represented by the following formula (where n is the number of repeating units):

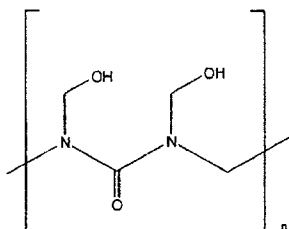


Commercially available polyvinylpyrrolidones have a pH of 3.0-7.0, as measured in a 5% w/v aqueous solution (USP monograph).

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Cross-linked polyvinylpyrrolidone, also known, *inter alia*, as polyplasdone, polyvinyl(poly)pyrrolidone and crosopovidone, is a preferred amido-group containing polymeric compound useful in the present invention. Cross-linked polyvinylpyrrolidone has a pH of 5.0-8.0 (1% aqueous suspension, NF). Other polymeric compounds, which are co-polymers containing vinylpyrrolidone monomer units are also useful in the compositions of the subject invention. The term "copolymer" as used herein includes polymers that include two or more distinct monomeric units. An example of such a copolymer containing vinylpyrrolidone monomer units is a copolymer of vinylpyrrolidone monomer units and vinyl acetate monomer units, such as copolyvidone.

Polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, and copolymers containing vinylpyrrolidone monomer units are examples of amido-group containing polymeric compounds in which the amido group is present in a pendant group attached to the polymeric backbone. Also useful in the present invention are amido-group containing polymeric compounds in which the amido group is present in the polymeric backbone. An example of such a polymeric compound is polynoxylin, which is a condensation product of formaldehyde and urea having the following structural formula (where n is the number of repeating units):



It is to be understood that the amido-group containing polymeric compounds useful to provide stabilized pharmaceutical compositions in accordance with the present invention are not to be construed as limited to the foregoing exemplary polymers. Thus, any pharmaceutically acceptable amido-group containing polymeric compound that provides a stabilized pharmaceutical composition of the present invention

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may be employed. Such pharmaceutically acceptable amido-group containing polymeric compounds are commercially available. For example, polyvinylpyrrolidone polymers are commercially available, for example, under the trade names **KOLLIDON®** and **PLASDONE®**; and, cross-linked polyvinylpyrrolidone polymers are commercially available, for example, under the trade names **KOLLIDON CL®**, **POLYPLASDONE XL®**, **POLYPLASDONE XL-10®** and **POLYPLASDONE INF-10®**. **KOLLIDON® K-30** is a particularly preferred polyvinylpyrrolidone polymer useful in the stabilized pharmaceutical compositions of the present invention.

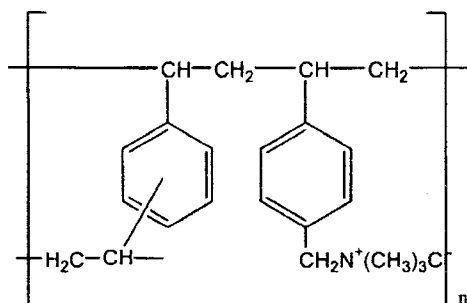
Polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, and copolymers containing vinylpyrrolidone monomer units used as the amido-group containing polymeric compound provide the additional advantage in that such compounds also can also function in the stabilized pharmaceutical compositions of the present invention in their conventional roles as excipients; for example, as binders, thickeners and disintegrants. In fact, use of these amido-group containing polymeric compounds can provide the additional advantage of requiring the addition of a lower amount, if any, lubricant to a composition of the subject invention, particularly when the composition is a solid dosage form such as a tablet. Moreover, when such amido-group containing polymeric compounds are used in the pharmaceutical compositions, it has also been found that the need to use separate fillers and disintegrants may be reduced or even eliminated.

The weight percentage of the amido-group containing polymeric compound required to provide a stabilized pharmaceutical composition of the subject invention is generally greater than the weight percentage of the amount of the polymeric compound that would be required to provide its conventional function as an excipient in the pharmaceutical composition such as a solid dosage form adapted for oral administration. Thus, the amido-group containing polymeric compounds are generally used in the pharmaceutical compositions of the subject invention in greater amounts than when used as conventional excipients.

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An amino-group containing polymeric compound is any pharmaceutically acceptable polymeric compound having, either in a pendant group attached to the polymer backbone, or as a component of the polymer backbone, an amino group as defined hereinabove.

A preferred amino-group containing polymeric compound is cholestyramine, having the following structural formula where n is the number of repeating units.



Cholestyramine is thus a copolymer of styrene (vinylbenzene) and divinylbenzene, containing about 2% divinylbenzene. Cholestyramine useful in the stabilized pharmaceutical compositions of the present invention is commercially available from different manufacturers under the tradenames, inter alia, **COLESTYRAMINE®**, **MK-135**, and **DOWEX 1-X2-Cl**. It is understood that the amino-group containing polymeric compounds can be any pharmaceutically acceptable amino-group containing polymeric compounds, or combination thereof.

The pharmaceutical compositions of the present invention will, therefore, generally contain between about 10 to about 99 percent; preferably between about 30 to about 80 percent by weight; and even more preferably, greater than about 30% by weight of the pharmaceutical composition of the amido-group or amino-group containing

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polymeric compound or combination thereof. Even more preferred yet are percentages of about 40% or greater by weight of the pharmaceutical composition. A particularly preferred percentage of the amido-group or amino-group containing polymeric compound, based on the weight of the pharmaceutical composition, will be greater than 40%.

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The pharmaceutical compositions of the present invention may also contain any pharmaceutically acceptable excipient or combination thereof. Conventional pharmaceutical excipients include those which function in a dosage form, for example, as a lubricant, glidant, diluent, binder, disintegrant, carrier, colorant or coating material.

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Examples of pharmaceutically acceptable excipients include, but are not limited to, lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, silicon dioxide, and microcrystalline cellulose.

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The preferred dosage forms of the stabilized pharmaceutical compositions of the present invention are solid dosage forms adapted for oral administration. However, within the scope of the dosage forms useful for formulating the stabilized compositions of the present invention include suspensions, solutions (drinkable and injectable) and emulsions. Tablet dosage forms are the particularly preferred solid dosage forms of the stabilized pharmaceutical compositions of the present invention. Tablet dosage forms may contain for example, as excipients, any pharmaceutically acceptable lubricant, binder, disintegrant, diluent, carrier, preservative or combination thereof. Solid dosage forms that are not formulated as tablets typically do not need a lubricant component since this is typically added to facilitate manufacture of tablet dosage forms. For the purpose of stable oral preparations of the present invention, pharmaceutically acceptable inert carriers can be either solid or liquid. Among other preferred dosage forms useful for formulating the stabilized pharmaceutical compositions of the present invention include powders, dispersible granules, dispersions, capsules, suspensions and cachets. Conventional methods of manufacturing these preferred dosage forms are employed. Thus, a tablet dosage form can be made, for example, by granulating the active component with or without an excipient, followed by addition of any other excipient(s) and then compression to form a tablet. The tablets are preferably made by direct compression methods as are

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known in the art. Excipients typically used in tablet dosage forms include carriers, lubricants, binders and fillers that facilitate compacting, shaping, and sizing. Examples of suitable lubricants include magnesium stearate, sodium stearyl fumarate, polyethylene glycol, stearic acid, hydrogenated vegetable oil and talc. Typical amount of lubricant used in a tablet dosage form range from about 0.1 to about 25% and preferably from about 0.25 to about 10% by weight of dosage form. In forming a powder preparation, a finely divided solid carrier is typically employed and is blended with finely divided active ingredient, and then filled into a packet, capsule, or any conventional device for containing the powder. Granular formulations may be similarly packaged. Suspensions or emulsions are obtained by suspending the active component, typically in the form of powder or granules, into a pharmaceutically acceptable liquid carrier which is conventionally adapted for administration orally or parenterally.

Stabilized pharmaceutical compositions of the invention have been produced wherein the only ingredients besides the active component were cross-linked polyvinylpyrrolidone and magnesium stearate. Tablets produced in this manner showed excellent stability in respect to lactone formation upon being subjected to a stability study at 40°C/75% relative humidity for up to six months. However, additional excipients may be beneficially added to obtain improvements in galenic or pharmaceutical parameters such as compressibility, flowability or appearance. Any pharmaceutically acceptable excipient can thus be added to a simple composition containing active component, amido-group containing polymeric compound and lubricant as desired.

An aqueous dispersion of a stabilized statin composition of the present invention will generally exhibit of a pH in the range of about 6.5 to about 10. It is preferred that an aqueous dispersion of a composition of the present invention exhibits a pH of not greater than about 10, preferably not greater than about 8. However, it is also possible to achieve aqueous dispersions of the stabilized statin compositions in accordance with the present invention which have a pH of not greater than about 6.5. Therefore, it is preferred that neither the amido-group containing polymeric stabilizer or amino-group containing polymeric stabilizer, or combination thereof, nor any additional excipient

results in a composition in which the pH of an aqueous dispersion thereof is greater than about 10, preferably not greater than about 8. It is particularly preferred that the amount of the amido-group or amino-group containing polymeric stabilizing compound, or combination thereof, does not alter the pH of an aqueous dispersion of a composition of the present invention by more than about one pH unit, relative to the pH of an aqueous dispersion of the same composition not containing the amido-group or amino-group containing polymeric compound or combination thereof.

A particularly preferred embodiment of the present invention provides a stabilized oral pharmaceutical formulation for treatment of dyslipidemia comprising the HMG-CoA reductase inhibitor atorvastatin calcium or pravastatin sodium as the active ingredient in a composition comprising a lubricant such as magnesium stearate and a stabilizing effective amount of an amido-group containing polymeric compound, such as cross-linked polyvinyl pyrrolidone, or a stabilizing effective amount of an amino-group containing polymeric compound, wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers. The preferred compositions are tablets made by conventional methods of direct compression.

In accordance with the present invention, the pharmaceutical compositions are useful for the treatment of dyslipidemia including, for example, hypercholesterolemia, hyperlipoproteinemia and/or hypertriglyceridemia. While one of ordinary skill in the art will understand that dosages will vary according to the particular requirements and bioavailability of the active ingredient, the indication, age of the patient, and other factors, the compositions of the present invention will generally be administered at a daily dosage of the active ingredient between about 10 to about 500 mg per day, and preferably about 10 mg to about 80 mg per day. As atorvastatin and pravastatin are suitable for once-daily dosing, preferably each unit dosage form will contain between about 10 mg and about 40 mg. In any event, the amount administered per dosage will be a therapeutically effective amount of the active components.

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EXAMPLES

The present invention will now be further explained in the following examples. However, the present invention should not be construed as limited thereby.

One of ordinary skill in the art will understand how to vary the exemplified preparations to obtain the desired results.

Example 1

A pravastatin formulation in the form of 150 mg tablets having the following composition was prepared as described below.

Ingredient	Percent By Weight
Pravastatin Sodium	6.67
Crospovidone	92.33
Magnesium Stearate	1.00

The crospovidone (cross-linked polyvinylpyrrolidone) used in Examples 1-5 and 8 is commercially available from the ISP Company (International Specialty Products), Wayne, NJ 07470 and is sold under the tradenames **POLYPLASDONE XL-10®** and **POLYPLASDONE INF-10®**. **POLYPLASDONE INF-10®** and **POLYPLASDONE XL-10®** are chemically identical materials, but have different particle size distributions, about 11 μm and about 30 μm , respectively.

Pravastatin sodium and polyplasdone were mixed in the dry state for 15 minutes and then magnesium stearate was added and the whole mixture was mixed for a further 5 minutes. Tablets were pressed from the mixture, each weighing approximately 150 mg. The pH of an aqueous dispersion of these tablets was 7.4.

Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 6 months, it was found that the tablets, including

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the pravastatin, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are presented in the table below:

Time (months)	0	1	2	3	4	6
Assay, %	103.6	103.4	100.4	102.7	100.6	100.5
Lactone, %	0.0	0.2	0.2	0.2	0.3	0.5

Example 2

A pravastatin formulation in the form of tablets having the following composition was prepared as described below.

Ingredient	Percent By Weight
Pravastatin Sodium	10.0
Crospovidone	12.0
Lactose Spray Dried	77.0
Magnesium Stearate	1.00

Pravastatin sodium and polyplasdone were premixed and sieved, lactose spray dried was added and the materials were mixed in a dry state for 20 minutes, then magnesium stearate was added and the whole mixed for a further 5 minutes. Tablets for all strengths were pressed from the mixture. Tablet weight for 10 mg strength was approximately 100 mg, for 20 mg strength approximately 200 mg, and for 40 mg strength approximately 400 mg. The pH of the aqueous dispersion was 7.0.

Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 3 months, it was found that the tablets, including the pravastatin, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are presented in the table below:

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Time (months)	0	1	2	3
Assay, %	98.7	98.7	100.4	97.5
Lactone, %	0.0	0.3	0.4	0.5

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Example 3

A pravastatin formulation in the form of tablets having the following composition was prepared as described in Example 2.

Ingredient	Percent By Weight
Pravastatin Sodium	10.0
Crospovidone	40.0
Lactose Spray Dried	49.0
Magnesium Stearate	1.00

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Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 6 months, it was found that the tablets, including the pravastatin, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are presented in the table below:

Time (months)	0	1	2	3	4	6
Assay, %	99.6	98.8	101.9	100.5	97.7	97.1
Lactone, %	0.0	0.3	0.4	0.6	0.5	0.8

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Example 4

A pravastatin formulation in the form of 100 mg tablets having the following composition was prepared as described below.

Ingredient	Percent By Weight
Pravastatin Sodium	10.0
Crospovidone	60.0
Microcrystalline Cellulose	29.0
Magnesium Stearate	1.00

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Pravastatin sodium and polyplasdone were premixed and sieved. Microcrystalline cellulose was added and the materials were mixed in a dry state for 15 minutes, then magnesium stearate was added and the whole mixed for a further 5 minutes. Tablets were pressed from the mixture. Tablet weight for 10 mg strength was approximately 100 mg. The pH of the aqueous dispersion was approximately 7.0.

Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 6 months, it was found that the tablets, including the pravastatin, remained substantially stable based on the weight percentage of lactone. The results of the stability study are presented in the table below:

Time (months)	0	1	2	6
Assay, %	101.8	101.2	103.1	96.1
Lactone, %	0.0	0.6	1.0	2.8

Example 5

An atorvastatin formulation in the form of 100 mg tablets having the following composition was prepared as described below.

Ingredient	Percent By Weight
Atorvastatin Calcium Trihydrate	10.84
Crospovidone	40.00
Lactose Spray Dried	48.16
Magnesium Stearate	1.00

Atorvastatin calcium trihydrate and polyplasdone were premixed and sieved. The lactose spray dried was added and the materials were mixed in a dry state for 10 minutes. Magnesium stearate was then added and the whole mixed for a further 5 minutes. Tablets were pressed from the mixture. Tablet weight for 10 mg strength was approximately 100 mg. The pH of the aqueous dispersion was 5.4.

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Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 3 months, it was found that the tablets, including the atorvastatin calcium, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are provided in the table below:

Time (months)	0	1	2	3
Assay, %	94.6	92.3	89.1	93.1
Lactone, %	0.33	0.31	0.45	0.45

Example 6

A pravastatin sodium formulation in the form of 10 mg tablets having the following composition was prepared as described below.

Ingredient	Percent By Weight
Pravastatin Sodium	10.0
Povidone (PVP K-30)	40.00
Lactose Spray Dried	48.16
Magnesium Stearate	1.00

The povidone (polyvinylpyrrolidone) used in Example 6 is commercially available from the BASF Corporation under the tradename **KOLLIDON K-30**.

Pravastatin sodium, lactose spray dried and povidone were premixed and sieved. These components were mixed in the dry state for about 15 minutes, after which magnesium stearate was added and further mixing conducted for about 5 minutes. Tablets were then pressed from the mixture. The approximate weight for a tablet containing 10 mg of pravastatin sodium was about 100 mg. The pH of an aqueous dispersion was approximately 6.6.

Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 3 months, it was found that the tablets, including

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the pravastatin, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are provided in the table below:

Time (months)	0	1	3
Assay, %	98.5	92.2	91.4
Lactone, %	0.0	1.5	2.8

Example 7

A pravastatin sodium formulation in the form of 10 mg tablets having the following composition was prepared as described below.

Ingredient	Percent By Weight
Pravastatin Sodium	10.0
Cholestyramine (Diolite AP 143/1093)	40.0
Lactose Spray Dried	49.0
Magnesium Stearate	1.0

Pravastatin sodium, lactose spray dried and cholestyramine were premixed and sieved. These components were mixed in the dry state for about 15 minutes, after which magnesium stearate was added and further mixing conducted for about 5 minutes. Tablets were then pressed from the mixture. The approximate weight for a tablet containing 10 mg of pravastatin sodium was about 100 mg. The pH of an aqueous dispersion was approximately 6.6.

Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 3 months, it was found that the tablets, including the pravastatin, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are provided in the table below:

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Time (months)	0	1	3
Assay, %	97.3	94.2	91.8
Lactone, %	0.0	0.5	0.9

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Example 8

An atorvastatin calcium formulation in the form of 10 mg tablets having the following composition was prepared as described below.

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Ingredient	Percent By Weight
Atorvastatin Calcium	7.0
Crospovidone	20.0
(POLYPLASDONE XL-10)	
Lactose Monohydrate	66.4
Povidone (PVP K-30)	3.3
Polysorbate 80	3.3
Alcohol 95% process solvent	

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Atorvastatin calcium, crospovidone, lactose monohydrate and povidone were premixed and granulated using an alcohol solution of the polysorbate 80. The granulate was then milled after which tablets were pressed from the milled granulate. The approximate weight for a tablet containing 10 mg of atorvastatin calcium was about 150 mg. The pH of an aqueous dispersion was approximately 6.6.

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Upon subjecting the so-formed tablets to a PVDC/PVC blister stability study at 40°C/75% relative humidity for 2 months, it was found that the tablets, including the atorvastatin calcium, remained substantially stable based on the weight percentage of lactone formation. The results of the stability study are provided in the table below:

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Time (months)	0	1	2
Assay, %	97.6	97.0	94.1
Lactone, %	0.6	0.4	0.7

5 Although certain presently preferred embodiments of the invention have
been described herein, it will be apparent to those skilled in the art to which the invention
pertains that variations and modifications of the described embodiments may be made
without departing from the spirit and scope of the invention. Accordingly, it is intended
that the invention be limited only to the extent required by the appended claims and the
10 applicable rules of law.

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What is claimed is:

1. A stabilized pharmaceutical composition for the treatment of dyslipidemia, comprising, as an active component, at least one ring-opened 7-substituted-3,5-dihydroxyheptanoic acid or ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or a pharmaceutically acceptable acid salt thereof, and a stabilizing effective amount of at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or combination thereof; wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers.
2. The composition of claim 1 wherein the at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or combination thereof, comprises between about 10 and about 99 percent by weight of the composition.
3. The composition of claim 2 wherein the at least one amido-group containing polymeric compound or at least one amino-group containing polymeric compound, or combination thereof, comprises between about 30 and about 80 percent by weight of the composition.
4. The composition of claim 1 wherein the active component comprises between about 0.05 and about 70 percent by weight of the composition.
5. The composition of claim 4 wherein the active component comprises between about 1 and about 60 percent by weight of the composition.
6. The composition of claim 1 wherein the active component is a pharmaceutically acceptable acid salt of pravastatin.
7. The composition of claim 6 wherein the pharmaceutically acceptable acid salt is pravastatin sodium.

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8. The composition of claim 1 wherein the active component is a pharmaceutically acceptable acid salt of atorvastatin.
9. The composition of claim 8 wherein the pharmaceutically acceptable acid salt is atorvastatin calcium.
10. The composition of claim 1 wherein the composition is in the form of a solid.
11. The composition of claim 10 wherein the composition is in the form of a tablet.
12. The composition of claim 11 wherein the tablet contains a lubricant.
13. The composition of claim 12 wherein the lubricant is selected from the group consisting of magnesium stearate, sodium stearyl fumarate, polyethylene glycol, stearic acid, hydrogenated vegetable oil and talc.
14. The composition of claim 10 wherein the composition is in the form of granules.
15. The composition of claim 14 wherein the granules are constituents of a dispersion.
16. The composition of claim 10 wherein the composition is in the form of a suspension.
17. The composition of claim 10 wherein the composition is in the form of a capsule.
18. The composition of claim 10 wherein the composition is in the form of a cachet.
19. The composition of claim 1 wherein the amido group in the amido-group containing polymeric compound or the amino group in the amino-group containing

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polymeric compound is present either in a pendant group attached to the backbone of the polymeric compound or as a component of the backbone of the polymeric compound.

20. The composition of claim 19 wherein the amido-group containing polymeric compound is selected from the group consisting of polyvinylpyrrolidone, cross-linked polyvinylpyrrolidone, copolymers of vinylpyrrolidone and vinyl acetate, and polynoxylin.

21. The composition of claim 1, wherein the amido-group containing polymeric compound or amino-group containing polymeric compound, or combination thereof, imparts a pH of not more than about 10 to an aqueous dispersion of said composition.

22. The composition of claim 21, wherein the amido-group containing polymeric compound or amino-group containing polymeric compound, or combination thereof, imparts a pH of not more than about 8 to an aqueous dispersion of said composition.

23. The composition of claim 19, wherein the amino-group containing polymeric compound is a quaternary ammonium group-containing polymeric compound.

24. The composition of claim 23, wherein the quaternary ammonium group-containing polymeric compound is cholestyramine.

25. The composition of claim 21 wherein the ring-opened 7-substituted-3,5-dihydroxyheptanoic acid or ring-opened 7-substituted-3,5-dihydroxyheptenoic acid, or pharmaceutically acceptable acid salt thereof, is a HMG-CoA reductase inhibitor medicament that is sensitive to a low pH environment.

26. A stabilized pharmaceutical composition for the treatment of dyslipidemia comprising, in admixture,

- (a) about 0.05% to about 70% by weight of a ring-opened 7-substituted 3,5-dihydroxyheptanoic acid or ring-opened 7-substituted-3,5-

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dihydroxyheptenoic acid or a pharmaceutically acceptable acid salt thereof,
and

- (b) about 30% to about 99% by weight of a stabilizing effective amount of an amido-group containing polymeric compound or a stabilizing effective amount of an amino-group containing polymeric compound, or combination thereof; wherein said stabilized pharmaceutical composition does not contain a stabilizing effective amount of another stabilizer or a combination of other stabilizers.

27. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid salt is pravastatin sodium.

28. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid salt is pravastatin sodium and the amido-group containing polymeric compound is cross-linked polyvinylpyrrolidone.

29. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid salt is pravastatin sodium and the amido-group containing polymeric compound is polyvinylpyrrolidone.

30. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid salt is pravastatin sodium and the amino-group containing polymeric compound is cholestyramine.

31. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid is atorvastatin calcium.

32. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid salt is atorvastatin calcium and the amido-group containing polymeric compound is cross-linked polyvinylpyrrolidone.

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33. The composition of claim 26, wherein the ring-opened 7-substituted 3,5-dihydroxy heptanoic acid salt is atorvastatin calcium and the amido-group containing polymeric compound is polyvinylpyrrolidone.

34. The composition of claim 26, in a solid tablet dosage form which further comprises a lubricant.

35. The composition of claim 34, wherein the lubricant is magnesium stearate.

36. A stabilized pharmaceutical composition comprising pravastatin sodium and about 40% or greater by weight of the composition of an amido-group or amino-group containing polymeric stabilizer.

37. A stabilized pharmaceutical composition comprising atorvastatin calcium and about 40% or greater by weight of the composition of an amido-group or amino-group containing polymeric stabilizer.

38. A method for the treatment of dyslipidemia, comprising the step of orally administering to a patient in need of such treatment a therapeutically effective unit dosage of the pharmaceutical composition of claim 1.

39. A method for the treatment of dyslipidemia, comprising the step of orally administering to a patient in need of such treatment a therapeutically effective unit dosage of the pharmaceutical composition of claim 26.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/11514

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/20, 9/26, 9/14, 9/48

US CL : 424/464, 465, 469, 470, 489, 451

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/464, 465, 469, 470, 489, 451

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

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

EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,180,589 A (JOSHI et al.) 19 January 1993, See entire document.	1-39
Y	US 5,582,838 A (RORK et al.) 10 December 1996, See entire document.	1-39
Y	US 6,147,090 a (DENINNO et al.) 14 November 2000. See entire document.	1-39
Y	US 6,207,664 B1 (HAYWARD et al.) 27 March 2001, See entire document.	1-39
Y	US 6,245,797 B1 (WINOKUR) 12 June 2001, See entire document.	1-39

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

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

14 JUNE 2001

Date of mailing of the international search report

14 SEP 2001

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