

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

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SUPERINDUSTRIA Y COMERCIO
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Tramite : 011 PCT-PATENT 379 FASE NACI 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: Expediente No. 03.107.810

Solicitud de patente titulada: "FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ACIDO [R-(R*,R*)]-2-(4-FLUOROFENIL)-β,δ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO) CARBONIL] -1H-PIRROL-1-HEPTANOICO (2:1)".

Solicitante: WARNER-LAMBERT COMPANY LLC.

RESPUESTA AL OFICIO NOTIFICADO POR FIJACION EN LISTA No. 205, DE FECHA
16 DE JULIO DE 2004 (OPOSICION)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma en mi carácter de apoderado de la sociedad en referencia, me permito manifestar lo siguiente ante la oposición interpuesta por Luis Fernando Rincón Cuellar, actuando como apoderado de la sociedad Procaps S.A., dentro del plazo legal previsto en el artículo 43 de la Decisión 486, en los siguientes términos:

1. a- El oponente pretende establecer que las Reivindicaciones 1 a 15 de la presente invención carecen de novedad y de nivel inventivo en virtud de las divulgaciones hechas por las anterioridades WO 97/03959, WO 97/03958 y WO 01/36384. El oponente dice:

"3.3. Con anterioridad a la fecha de prioridad de esta solicitud, la molécula de la atorvastatina ya era parte del estado de la técnica tal y como lo referencia el mismo solicitante en su texto descriptivo cuando hace referencia al estado del arte anterior. Adicionalmente, a la fecha de prioridad de la solicitud colombiana el estado de la técnica ya revelaba los siguientes documentos en los cuales se ha estudiado la conformación de la molécula de atorvastatina amorfa en atorvastatina cristalina:

- D1: WO 9703959, del 6 de febrero de 1997.
- D2: WO 9703958, del 6 de febrero de 1997.
- D3: WO 0136384, del 25 de mayo de 2001.

3.4. La solicitud D1 y D2, del mismo solicitante, se refieren a formas cristalinas de atorvastatina conocida con el nombre de hemisal de calcio de ácido $[R-(R^*, R^*)]-2-(4\text{-fluorofenil})\text{-beta, delta -dihidroxi-5-(1-metiletil)-3-fenil-4-}[(\text{fenilamino})\text{carbonil}]\text{-1H-pirrol-1-heptanoico}$ designado como una Forma I, Forma II y Forma IV en el D1 y la Forma III en el D2, caracterizados por tener un patrón de difracción de rayos X en polvo y/o en estado sólido, así como los métodos para la preparación y la composición farmacéutica del mismo, que es útil como agentes para tratar la hiperlipidemia y la hipercolesterolemia.

3.5. Como se puede apreciar a simple vista, el arte anterior descrito en estas solicitudes D1 y D2, ya revelaba un compuesto farmacéutico que comprendía unas formas cristalinas de atorvastatina.

3.6. Adicionalmente y como es de conocimiento general en la, técnica, una forma cristalina representa un ordenamiento en el espacio o red cristalina del una estructura química (fenómeno denominado "Poliformismo"(sic)), de tal suerte, que sólo se requiere conjugar apropiadamente las condiciones de cristalización de un compuesto conocido para obtener un polimorfo derivado. Por lo tanto, aún alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. El poliformismo (sic) es una técnica conocida desde 1788 (Martin Klaproth) para hacer pasar la molécula de una forma a otra.

3.7. Ahora bien, si combinamos el conocimiento indicado en estas solicitudes D1 y D2, y el conocimiento general de la técnica que dicta que las modificaciones polimórficas de un compuesto, en general pueden alterar algunas propiedades de las moléculas tales como su forma cristalina, velocidad de disolución, punto de fusión, densidad verdadera, dureza y/o fragilidad cristalina, el espectro de

absorción infrarrojo o el difractograma de rayos X entre otros, indudablemente es posible derivar Formas Cristalinas V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX de atorvastatina o un hidrato de la misma, que tiene un patrón de difracción de rayos X en polvo. Es obvio, pues es de general conocimiento que algunas de estas modificaciones, en especial la alteración en la velocidad de disolución, causan diferencias en la absorción y por supuesto en los niveles de Biodisponibilidad de un medicamento presentado en forma sólida, sin implicar que exista una diferencia sustancial frente al mismo medicamento presentado en forma de solución. Así las cosas, lo expuesto en la solicitud colombiana 03-107810 en las reivindicaciones 1 a 15, se deriva evidentemente del arte anterior y es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del conocimiento revelado en las solicitudes D1 y D2 en conjunto con el conocimiento general de la técnica, afecta de manera directa el requisito de altura inventiva de la solicitud colombiana que se pretenden proteger.

3.8. Ahora bien, la solicitud D3 de Teva, también se refiere a formas cristalinas de atorvastatina designado como una Forma V, caracterizado por tener un patrón de difracción de rayos X en polvo y/o en estado sólido. Según se describe en este documento, D1, se revela una forma cristalina de atorvastatina que tiene un patrón de difracción de rayos X en polvo que contiene los valores según la figura 1.

(...)

3.9. Como se nota, la solicitud colombiana hace referencia a la misma molécula del documento D3, demostrando que alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto. Así las cosas, la solicitud colombiana objeto de la, presente oposición no es novedosa desde ningún punto de vista, pues a todas luces lo que allí se describe ya se revelaba con anterioridad en la solicitud previa D3; por lo tanto consideramos que la concesión de esta solicitud colombiana atentaría abiertamente contra la normatividad colombiana, que explícitamente consagra a la NOVEDAD como uno de los tres elementos esenciales para que de a lugar la concesión de una patente."

b- Respetuosamente difiero rotundamente de las apreciaciones hechas por el oponente, puesto que se basan en un erróneo entendimiento de los criterios de novedad y nivel inventivo.

2. a- En cuanto a la novedad, me parece importante establecer claramente el alcance de dicho requisito. El artículo 16 de la Decisión 486 dice, en parte, lo siguiente:

"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."

Es decir, una invención es nueva cuando no ha sido divulgada por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la

solicitud de patente o, de la prioridad reconocida. Claro está que, para desvirtuar la novedad de una invención, la divulgación no debe ser cualquiera, sino debe ser una divulgación **detallada y suficiente** para que una persona medianamente versada en el arte pueda reproducir perfectamente la invención a la que se le pretende desvirtuar la novedad. Por lo tanto, dicha divulgación debe comprender todas y cada una de las características específicas de la solicitud en estudio y haberlas descrito específicamente como las ilustra y pretende reclamar la solicitud al que se le pretende desvirtuar la novedad. Así lo ha planteado el Tribunal Andino de Justicia al decir:

“Lo novedoso es lo que no está comprendido en el estado de la técnica (divulgación cualificada) o lo que no haya sido divulgado o hecho accesible al público en cualquier lugar (divulgación simple y novedad absoluta). La divulgación puede ser oral o escrita, puede resultar del uso o explotación, o producirse por cualquier otro medio. Esta divulgación debe ser **detallada** y, en todo caso, **suficiente** para que una persona del oficio pueda realizar esa información para ejecutar o explotar la invención...” (Proceso 12-IP-98) (subrayado y negrilla propia)

b- El objeto de la presente invención es proporcionar las **nuevas formas cristalinas de atorvastatina**, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII, XIX o un hidrato de los mismos, caracterizados por el patrón de difracción en polvo de rayos X.

Los compuestos que presentan estructuras amorfas, generalmente no son comercializados, debido a que como son distribuciones desordenadas no se pueden identificar por sus hábitos a pesar de que exhiban propiedades farmacológicas deseables puesto que son inestables tanto química como físicamente. Es por esto que actualmente existe un interés en el sector farmacéutico primordialmente, por caracterizar el mayor número de polimorfos posibles que presente un compuesto. El objetivo es establecer cuál polimorfo tiene las propiedades más apropiadas, tales como tamaño de partícula, velocidad de disolución, solubilidad, biodisponibilidad y estabilidad. Es imposible conocer *a priori* las formas cristalinas que pueda formar un compuesto químico en estado sólido, y de igual manera es imposible predecir cuál de esta forma cristalina será estable y poseerá las características más apropiadas para su formulación.

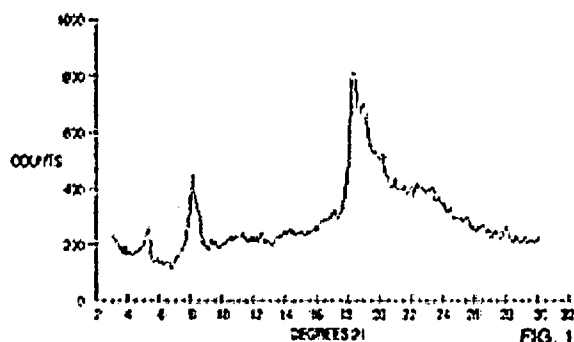
c- Ninguno de los documentos citados por el oponente anticipa de forma detallada y suficiente las formas cristalinas **específicas** reclamadas por la presente invención, de tal forma que una persona medianamente versada en el arte pueda reproducirlas.

En cuanto al documento D3 particularmente, éste divulga una “supuesta” nueva forma cristalina de la sal calcio de atorvastatina: Forma V; al analizar su difractograma, los picos 2θ presentan **rangos**

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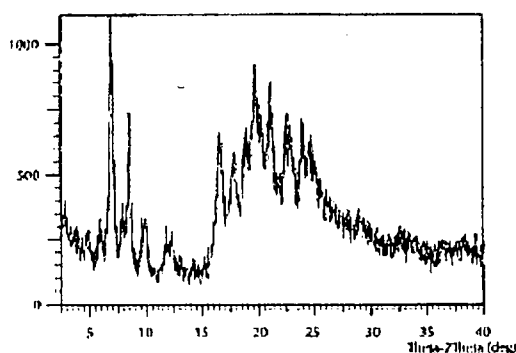
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supremamente amplios los cuales se pueden apreciar en la página 5 –líneas 13 a 15, entre los grados 2θ , 8 y 23:



Contrario a lo anterior, si se examina el difractograma en polvo de rayos-X para la forma V divulgada por la presente invención se tiene lo siguiente:

FIG. 1



Comparando el difractograma efectuado en la presente invención para la forma V, frente al difractograma divulgado en el documento D3 citado por el oponente, claramente se puede observar que el difractograma de la presente invención presenta picos con alta resolución, es decir, picos diferenciables unos de los otros, por lo tanto se puede concluir que esta forma presenta un patrón de empaquetamiento **ordenado**: una forma crystalina; mientras que el difractograma presentado en el documento D3 presenta rangos de grados 2θ amplios, baja resolución de los picos, lo cual representa un patrón de empaquetamiento **desordenado**, es decir una forma amorfa.

d- En conclusión, la presente invención presenta **nuevas** formas cristalinas de atorvastatina y como se demostró, no existe una coincidencia estructural, al analizar las estructuras tridimensionales de las nuevas formas cristalinas con lo divulgado en el estado de la técnica. Me permito solicitarle al Examinador respetuosamente tener en cuenta los anteriores argumentos en el momento de realizar su Examen de Fondo para evaluar el criterio de novedad.

3. a- En cuanto al nivel inventivo, el artículo 18 de la Decisión 486 establece que una invención demuestra nivel inventivo si no resulta obvia o no se deriva de manera evidente del estado de la técnica para una persona medianamente versada en el arte. ¿Qué es lo obvio o lo que se deriva de manera evidente? Lo obvio o lo que se deriva de manera evidente es aquello que no necesita de prueba alguna para saber su resultado, o porque existen instrucciones específicas para su obtención o porque existen sugerencias tan claras y precisas que no podría haber otro resultado posible. Es decir, cuando no existen instrucciones específicas que apunten al resultado que se evalúa o, inclusive existiendo sugerencias sobre dicho posible resultado, existe la posibilidad que dichas sugerencias pudieran producir varios otros resultados, es claro que el resultado o invento evaluado sí tiene nivel inventivo.

Adicionalmente, en relación con el alcance del requisito de nivel inventivo, el Tribunal Andino de Justicia (TAJ) ha establecido lo siguiente:

“Surge por consiguiente un requisito adicional al de la novedad: el nivel inventivo, del cual se desprende que la invención, además de no ser obvia para un experto medio, debe ser siempre el resultado de una actividad creativa del hombre, sin que ello signifique que para alcanzar la regla técnica propuesta, no se puedan utilizar procedimientos o métodos comunes o ya conocidos en el área técnica correspondiente. Específicamente en el área de los inventos químicos y biotecnológicos, sucede con frecuencia que aplicando procedimientos conocidos pueden obtenerse resultados inesperados para una persona normalmente versada en la materia. Por ello, el juicio del nivel inventivo no puede ser elaborado con criterios generales, sino que dependerá de las especiales circunstancias de cada caso.”¹ (Subrayado y negrilla fuera de texto).

Es decir, el hecho que una herramienta conocida en el estado de la técnica sea utilizada como mecanismo o punto de partida para llegar a una solución particular, no necesariamente convierte su utilización y los resultados específicos obtenidos de la misma en evidentes para una persona medianamente versada en el arte. Para determinar la existencia de nivel inventivo se tienen que apreciar las circunstancias particulares del caso, en especial las diferencias que se presentan entre el invento y el estado de la técnica, tomando en cuenta que aunque se utilicen herramientas o procedimientos conocidos en el arte para llegar al resultado inventivo, es el resultado, es decir, el invento, el que debe ser inesperado, no obvio, ni derivarse del estado de la técnica, más no las herramientas utilizadas para llegar a dicho invento.

¹ Proceso 105-IP-2000.

b- Ahora bien, analizando los documentos citados por el oponente, éstos ni divulgan ni sugieren, ya sea de forma individual o en combinación, las nuevas formas cristalinas de la presente invención y mucho menos sus beneficios. Es imposible para una persona medianamente en el arte determinar, *a priori*, que un nuevo polimorfo exista y mucho menos determinar con algún grado de certeza su estructura tridimensional exacta, sus propiedades fisicoquímicas (tales como velocidad de disolución, solubilidad, biodisponibilidad, y estabilidad) y su actividad biológica. Es ampliamente conocido para cualquier persona medianamente versada en el arte que no es posible predecir la existencia de nuevos polimorfos de un compuesto en particular, incluso si ya se conocen formas cristalinas del compuesto, como ocurre en el presente caso. Algunos compuestos en estado sólido presentan una o más formas cristalinas, pero no existe un método conocido que pueda predecir las formas cristalinas que pueda presentar un compuesto en particular.

A forma de ejemplo representativo de las nuevas formas cristalinas de la p
Forma VII presenta los siguientes beneficios: (los beneficios de otras f
atorvastatina se encuentran en las páginas 66 a 67)

10.20.1.11 /

Patentes

i) Tiene una muy buena estabilidad química, comparable con la Forma I. Como las formas no cristalinas de atorvastatina no son estables químicamente, esto es una ventaja significativa que se traduciría en una vida media aumentada y una fecha de caducidad posterior.

ii) Se puede preparar a partir de solventes no-tóxicos, como lo es el sistema acetona/agua, mientras que la Forma I se prepara en el sistema de metanol/agua.

iii) Contiene menos agua, se encuentra en la forma de sesquihidrato, lo cual significa que un peso unitario de esta forma contiene más moléculas de atorvastatina, es decir, posee mayor potencia.

iv) Tiene mejores propiedades para el tableteo (es menos quebradizo) al compararlo con la Forma I. Tiene un Índice de Fractura Brittle, BFI, de 0,09, mientras que la Forma I tiene un valor de BFI de 0,81 (valga la pena aclarar que el BFI refleja la fragilidad y varía de 0 –bueno, baja fragilidad-, a 1 –deficiente, alta fragilidad-). Esta menor fragilidad indica una mayor facilidad de fabricación de los comprimidos.

c- En el presente caso es claro que nos encontramos ante un resultado sorprendentemente inesperado, el cual de ninguna manera sería obvio para una persona medianamente versada en el arte, ni evidente a partir del estado del arte. El hecho de que para una

persona medianamente versada en el arte resulte obvio intentar desarrollar nuevas formas cristalinas para un compuesto en estado sólido conocido, no necesariamente convierte en obvia un nuevo polimorfo en particular que proporcione beneficios varios. El "obvio intentar" no convierte el resultado de una investigación en evidente, especialmente en las ciencias químicas, donde incluso pequeños cambios en la estructura tridimensional de un compuesto pueden tener grandes efectos en el resultado final, efectos que en la práctica no son predecibles. La práctica de "prueba y error" utilizada comúnmente por los investigadores para el desarrollo de nuevas formas cristalinas es simplemente una herramienta conocida, por medio de la cual se pueden obtener resultados inesperados. La mayoría de los ensayos no resultan en nuevos polimorfos por múltiples razones, pero éstos casos raramente se dan a conocer.

4. Solicito respetuosamente al Despacho que al momento de hacer el estudio de patentabilidad pertinente, tenga en cuenta los argumentos aquí presentes para desestimar la oposición presentada, puesto que claramente carece de fundamentos para prosperar y deslegitimar la solicitud de patente de invención en estudio.

5. Aprovecho la presente oportunidad para poner en conocimiento del Despacho mi cambio de oficina, por lo que de ahora en adelante, recibiré notificaciones en la Calle 100 No. 8A-37 Torre A, Piso 10, World Trade Center, o en la secretaría de ese Despacho.

Atentamente,



CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295
ANEXO: DISKETTE

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 107810

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION -**
PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **538**,
DE FECHA **31 DE MARZO DE 2004**, EL TERMINO HABIL SEÑALADO POR LA
LEY EXPIRA EL **01 DE JULIO DE 2004**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☒ _____

NO ☐ _____



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 207/34, A61K 31/40	A1	(11) International Publication Number: WO 97/03959 (43) International Publication Date: 6 February 1997 (06.02.97)
(21) International Application Number: PCT/US96/11368 (22) International Filing Date: 8 July 1996 (08.07.96) (30) Priority Data: 60/001,452 17 July 1995 (17.07.95) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BRIGGS, Christopher, A. [US/US]; 643 East 12th Street, Holland, MI 49423 (US). JENNINGS, Rex, Allen [US/US]; 405 Lincoln Avenue, Holland, MI 49423 (US). WADE, Robert, A. [US/US]; 3882 62nd Street, Holland, MI 49423 (US). HARASAWA, Kikuko [JP/JP]; 202 Liberty Palace Odakyusagamihara, 18-15, Minamidai 6-chome, Sagamihara-shi, Kanagawa 228 (JP). ICHIKAWA, Shigeru [JP/JP]; D-403 CI-Heights, 1356 Yamasaki-cho, Machida-shi, Tokyo 195 (JP). MINOHARA, Kazuo [JP/JP]; 702 Park-Heights Sagamihara, 4-4, Sagami-hara 5-chome, Sagamihara-shi, Kanagawa 229 (JP). NAKA-GAWA, Shinsuke [JP/JP]; 303 Seishin-Hills, 14-30, Seishin 7-chome, Sagamihara-shi, Kanagawa 229 (JP).		(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al. (81) Designated States: AU, BG, BR, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)		
(57) Abstract Novel crystalline forms of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt designated Form I, Form II, and Form IV are characterized by their X-ray powder diffraction and/or solid state NMR are described, as well as methods for the preparation and pharmaceutical composition of the same, which are useful as agents for treating hyperlipidemia and hypercholesterolemia.		

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FR	France			UZ	Uzbekistan

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CRYSTALLINE [R-(R*,R*)]-2-(4-FLUOROPHENYL)-BETA,DELTA-DIHYDROXY-5-(1-METHYLETHYL)-3-PHENYL-4-[(PHENYLAMINO)CARBONYL]-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)

10

BACKGROUND OF THE INVENTION

The present invention relates to novel crystalline forms of atorvastatin which is known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compounds of the present invention are useful as inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and are thus useful hypolipidemic and hypocholesterolemic agents.

25

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans ($\pm$)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

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United States Patent Number 5,273,995, which is herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-

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-2-

methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

United States Patent Numbers 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, which are herein incorporated by reference, disclose various processes and key intermediates for preparing atorvastatin.

Atorvastatin is prepared as its calcium salt, i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The calcium salt is desirable since it enables atorvastatin to be conveniently formulated in, for example, tablets, capsules, lozenges, powders, and the like for oral administration. Additionally, there is a need to produce atorvastatin in a pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications.

Furthermore, the process by which atorvastatin is produced needs to be one which is amenable to large-scale production. Additionally, it is desirable that the product should be in a form that is readily filterable and easily dried. Finally, it is economically desirable that the product be stable for extended periods of time without the need for specialized storage conditions.

The processes in the above United States Patents disclose amorphous atorvastatin which has unsuitable filtration and drying characteristics for large-scale production and must be protected from heat, light, oxygen, and moisture.

We have now surprisingly and unexpectedly found that atorvastatin can be prepared in crystalline form. Thus, the present invention provides atorvastatin in new crystalline forms designated Form I, Form II, and

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Form IV. Form I atorvastatin consists of smaller particles and a more uniform size distribution than the previous amorphous product and exhibits more favorable filtration and drying characteristics. Additionally, Form I atorvastatin is purer and more stable than the amorphous product.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

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	2 θ	d	Relative Intensity (>20%) Ground 2 Minutes
	9.150	9.6565	42.60
	9.470	9.3311	41.94
	10.266	8.6098	55.67
5	10.560	8.3705	29.33
	11.853	7.4601	41.74
	12.195	7.2518	24.62
	17.075	5.1887	60.12
	19.485	4.5520	73.59
10	21.626	4.1059	100.00
	21.960	4.0442	49.44
	22.748	3.9059	45.85
	23.335	3.8088	44.72
	23.734	3.7457	63.04
15	24.438	3.6394	21.10
	28.915	3.0853	23.42
	29.234	3.0524	23.36

20 Further, the present invention is directed to
crystalline Form I atorvastatin and hydrates thereof
characterized by the following solid-state ^{13}C nuclear
magnetic resonance spectrum wherein chemical shift is
expressed in parts per million measured on a Bruker
25 AX-250 spectrometer:

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	Assignment (7 kHz)	Chemical Shift
	C12 or C25	182.8
	C12 or C25	178.4
5	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	137.0
		134.9
		131.1
10		129.5
		127.6
		123.5
		120.9
		118.2
15		113.8
	C8,C10	73.1
		70.5
		68.1
		64.9
20	Methylene Carbons	
	C6, C7, C9, C11	47.4
		41.9
		40.2
	C33	26.4
25		25.2
	C34	21.3

30 In a preferred embodiment of the first aspect of the invention, crystalline Form I atorvastatin is a trihydrate.

In a second aspect, the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray

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powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding and measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

	2θ	d	Relative Intensity (>20%) Ground 2 Minutes
	5.582	15.8180	42.00
	7.384	11.9620	38.63
10	8.533	10.3534	100.00
	9.040	9.7741	92.06
	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
15	19.490	4.5507	56.64
	20.502	4.3283	67.20
	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
20	29.504	3.0250	37.86

Further, the second aspect of the present invention is directed to crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:

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		Assignment	Chemical Shift
5		Spinning Side Band	209.1
		Spinning Side Band	206.8
		C12 or C25	181 (broad)
		C12 or C25	163 (broad)
		C16	161 (broad)
		Aromatic Carbons	
10		C2-C5, C13-C18, C19-C24, C27-C32	140.5
			134.8
			133.3
			129.0
			122.9
15			121.4
			120.3
			119.0
			117.1
			115.7
20			114.7
		C8, C10	70.6
			69.0
			68.0
			67.3
25		Spinning Side Band	49.4
		Spinning Side Band	48.9
		Methylene Carbons	
		C6, C7, C9, C11	43.4
			42.3
30			41.7
			40.2
		C33	27.5
		C34	22.8 (broad)

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In a third aspect, the present invention is directed to crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >15% measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

	2θ	d	Relative Intensity (>15%)
10	4.889	18.605	38.45
	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
15	10.416	8.4859	20.00
	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
20	19.569	4.5327	54.79
	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23

Further, the fourth aspect of the present invention is directed to Form IV atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed as parts per million measured on a Bruker AX-250 spectrometer:

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	Assignment	Chemical Shift
	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad) and 159.0 (broad)
5	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
10	C8, C10	71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9

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As inhibitors of HMG-CoA, the novel crystalline forms of atorvastatin are useful hypolipidemic and hypocholesterolemic agents.

5 A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of crystalline Form I, Form II, or Form IV atorvastatin in unit dosage form in the treatment methods mentioned above. Finally, the present invention is directed to methods
10 for production of Form I, Form II, or Form IV atorvastatin.

BRIEF DESCRIPTION OF THE DRAWINGS

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The invention is further described by the following nonlimiting examples which refer to the accompanying Figures 1 to 6, short particulars of which are given below.

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Figure 1

Diffractiongram of Form I atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 3767.50 counts per second (cps))

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Figure 2

Diffractiongram of Form II atorvastatin ground for 2 minutes (Y-axis = 0 to maximum intensity of 1500 cps)

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Figure 3

Diffractiongram of Form IV atorvastatin (Y-axis = 0 to maximum intensity of 8212.5 cps).

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Figure 4

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form I atorvastatin.

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Figure 5

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form II atorvastatin.

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Figure 6

Solid-state ^{13}C nuclear magnetic resonance spectrum with spinning side bands identified by an asterisk of Form IV atorvastatin.

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DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form I, Form II, or Form IV atorvastatin may be characterized by their X-ray powder diffraction patterns and/or by their solid state nuclear magnetic resonance spectra (NMR).

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X-RAY POWDER DIFFRACTION

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Forms I, II, and IV Atorvastatin

Forms I, II, or Form IV atorvastatin were characterized by their X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns of Forms I, II, and Form IV atorvastatin were measured on a Siemens D-500 diffractometer with CuK_α radiation.

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Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).

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CuK_a radiation (20 mA, 40 kV, $\lambda = 1.5406 \text{ \AA}$) slits I and II at 1°) electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at 1° and IV at 0.15°).

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Methodology

The silicon standard is run each day to check the X-ray tube alignment.

Continuous $\theta/2\theta$ coupled scan: 4.00° to 40.00° in 2θ , scan rate of 6°/min: 0.4 sec/0.04° step.

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Sample tapped out of vial and pressed onto zero-background quartz in aluminum holder. Sample width 13-15 mm.

Samples are stored and run at room temperature.

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Grinding/Sieving

Grinding is used to minimize intensity variations for the diffractogram disclosed herein. However, if grinding significantly altered the diffractogram or increased the amorphous content of the sample, then the diffractogram of the unground sample was used. Grinding was done in a small agate mortar and pestle. The mortar was held during the grinding and light pressure was applied to the pestle.

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Ground Form II atorvastatin was sieved through a 230 mesh screen before analysis by x-ray diffraction.

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Table 1 lists the 2θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >20% for crystalline Form I atorvastatin. Table 1 also lists the relative intensities of the same lines in a diffractogram measured after 2 minutes of grinding. The intensities of the sample ground for 2 minutes are more

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representative of the diffraction pattern without preferred orientation. It should also be noted that the computer-generated, unrounded numbers are listed in this table.

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TABLE 1. Intensities and Peak Locations of all Diffraction Lines With Relative Intensity Greater Than 20% for Form I Atorvastatin

	2 θ	d	Relative Intensity (>20%) No Grinding	Relative Intensity (>20%)* Ground 2 Minutes
	9.150	9.6565	37.42	42.60
	9.470	9.3311	46.81	41.94
	10.266	8.6098	75.61	55.67
	10.560	8.3705	24.03	29.33
15	11.853	7.4601	55.16	41.74
	12.195	7.2518	20.03	24.62
	17.075	5.1887	25.95	60.12
	19.485	4.5520	89.93	73.59
	21.626	4.1059	100.00	100.00
20	21.960	4.0442	58.64	49.44
	22.748	3.9059	36.95	45.85
	23.335	3.8088	31.76	44.72
	23.734	3.7457	87.55	63.04
	24.438	3.6394	23.14	21.10
25	28.915	3.0853	21.59	23.42
	29.234	3.0524	20.45	23.36

* The second relative intensity column gives the relative intensities of the diffraction lines on the original diffractogram after 2 minutes of grinding.

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Table 2 lists the 2 θ , d-spacings, and relative intensities of all lines in the ground/sieved sample

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with a relative intensity of >20% for crystalline Form II atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

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TABLE 2. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 20% for Form II Atorvastatin

	2 θ	d	Relative Intensity (>20%)
10	5.582	15.8180	42.00
	7.384	11.9620	38.63
	8.533	10.3534	100.00
	9.040	9.7741	92.06
15	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
	19.490	4.5507	56.64
	20.502	4.3283	67.20
20	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
	29.504	3.0250	37.86

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Table 3 lists the 2 θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of >15% for crystalline Form IV atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this

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table.

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TABLE 3. Intensities and Peak Locations of All
Diffraction Lines With Relative Intensity
Greater Than 15% for Form IV Atorvastatin

	2 θ	d	Relative Intensity (>15%)
5	4.889	18.605	38.45
	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
10	10.416	8.4859	20.00
	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
15	19.569	4.5327	54.79
	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23
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SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

25 Methodology

All solid-state ^{13}C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The magic-angle was adjusted using the Br signal of KBr by detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res.,

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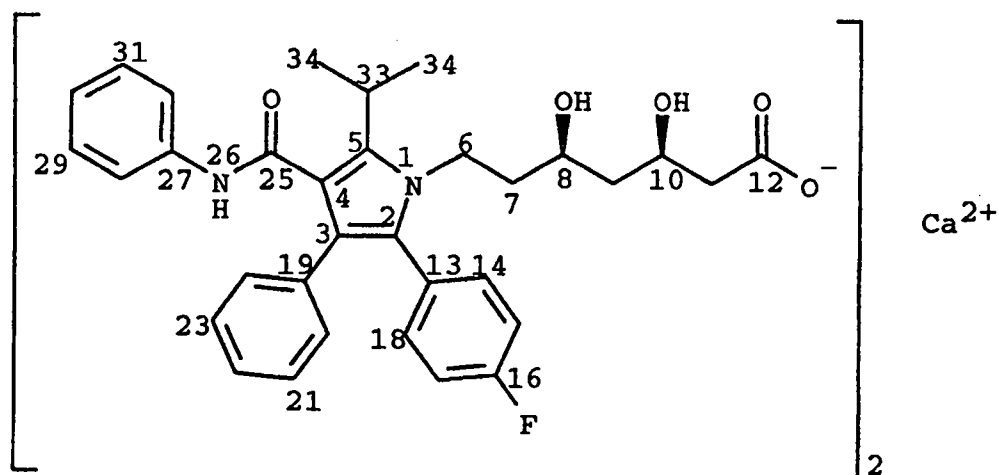
1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988;76:54).

Table 4 shows the solid-state NMR spectrum for crystalline Form I atorvastatin.

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TABLE 4. Carbon Atom Assignment and Chemical Shift for Form I Atorvastatin

5	Assignment (7 kHz)	Chemical Shift
	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	137.0
10		134.9
		131.1
		129.5
		127.6
		123.5
15		120.9
		118.2
		113.8
	C8, C10	73.1
		70.5
20		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
		41.9
25		40.2
	C33	26.4
		25.2
	C34	21.3

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Table 5 shows the solid-state NMR spectrum for crystalline Form II atorvastatin.

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TABLE 5. Carbon Atom Assignment and Chemical Shift for Form II Atorvastatin

Assignment		Chemical Shift
5	Spinning Side Band	209.1
	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
	C16	161 (broad)
Aromatic Carbons		
10	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
		129.0
		122.9
15		121.4
		120.3
		119.0
		117.1
		115.7
20		114.7
		70.6
		69.0
	C8, C10	68.0
		67.3
25	Spinning Side Band	49.4
	Spinning Side Band	48.9
Methylene Carbons		
30	C6, C7, C9, C11	43.4
		42.3
		41.7
		40.2
	C33	27.5
	C34	22.8 (broad)

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Table 6 shows the solid-state NMR spectrum for crystalline Form IV atorvastatin.

5	TABLE 6. Carbon Atom Assignment and Chemical Shift for Form IV Atorvastatin	
	Assignment	Chemical Shift
	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad) and 159.0 (broad)
10	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
15	C8, C10	
		71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9

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Crystalline Form I, Form II, and Form IV atorvastatin of the present invention may exist in anhydrous forms as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be encompassed within the scope of the present invention. Crystalline Form I atorvastatin contains about 1 to 8 mol of water. Preferably, Form I atorvastatin contains 3 mol of water.

The present invention provides a process for the preparation of crystalline Form I atorvastatin which comprises crystallizing atorvastatin from a solution in solvents under conditions which yield crystalline Form I atorvastatin.

The precise conditions under which crystalline Form I atorvastatin is formed may be empirically determined and it is only possible to give a number of methods which have been found to be suitable in practice.

Thus, for example, crystalline Form I atorvastatin may be prepared by crystallization under controlled conditions. In particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

When the starting material for the preparation of the desired crystalline Form I atorvastatin is a solution of the corresponding sodium salt, one preferred preparation involves treating a solution of the sodium salt in water containing not less than about 5% v/v methanol, preferably about 5% to 33% v/v

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methanol, particularly preferred about 10% to 15% v/v methanol, with an aqueous solution of calcium acetate, preferably at an elevated temperature at up to about 70°C such as, for example, about 45-60°C, particularly preferred about 47-52°C. It is preferable to use calcium acetate and, in general, 1 mole of calcium acetate to 2 moles of the sodium salt of atorvastatin. Under these conditions, calcium salt formation as well as crystallization should preferably be carried out at an elevated temperature, for example within the above-mentioned temperature ranges. It has been found that it may be advantageous to include in the starting solution a small amount of methyl tert-butyl ether (MTBE) such as, for example, about 7% w/w. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin to the crystallization solution in order to consistently produce crystalline Form I atorvastatin.

When the starting material is amorphous atorvastatin or a combination of amorphous and crystalline Form I Atorvastatin, the desired crystalline Form I atorvastatin may be obtained by suspending the solid in water containing up to about 40% v/v, such as, for example, about 0% to 20% v/v, particularly preferred about 5% to 15% v/v co-solvent such as, for example, methanol, ethanol, 2-propanol, acetone, and the like until conversion to the required form is complete, followed by filtration. It has frequently been found desirable to add "seeds" of crystalline Form I atorvastatin to the suspension in order to ensure complete conversion to crystalline Form I atorvastatin. Alternatively, a water-wet cake consisting principally of amorphous atorvastatin can be heated at elevated temperatures such as, for example, up to about 75°C, particularly preferred about 65-70°C, until a significant amount of crystalline Form I

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atorvastatin is present, whereupon the amorphous/
crystalline Form I mixture can be slurried as described
above.

Crystalline Form I atorvastatin is significantly
5 easier to isolate than amorphous atorvastatin and can
be filtered from the crystallization medium after
cooling, and washed and dried. For example, filtration
of a 50 mL slurry of crystalline Form I atorvastatin
was complete within 10 seconds. A similarly sized
10 sample of amorphous atorvastatin took more than an hour
to filter.

The present invention also provides a process for
the preparation of crystalline Form II atorvastatin
which comprises suspending atorvastatin in solvents
15 under conditions which yield crystalline Form II
atorvastatin.

The precise conditions under which Form II of
crystalline atorvastatin is formed may be empirically
determined and it is only possible to give a method
20 which has been found to be suitable in practice.

Thus, for example, when the starting material is
amorphous, a combination of amorphous and Form I, or
crystalline Form I atorvastatin, the desired Form II of
crystalline atorvastatin may be obtained by suspending
25 the solid in methanol containing about 40% to about 50%
water until conversion to the required form is
complete, followed by filtration.

The present invention also provides a process for
the preparation of crystalline Form IV atorvastatin
30 which comprises crystallizing atorvastatin from a
solution thereof in solvents under conditions which
yield crystalline Form IV atorvastatin.

The precise conditions under which Form IV of
crystalline atorvastatin is formed may be empirically
35 determined and it is only possible to give a method
which has been found to be suitable in practice.

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Thus, for example, when the starting material is Form I of crystalline atorvastatin, the desired Form IV of crystalline atorvastatin may be obtained by dissolving the solid in methanol whereupon crystalline Form IV precipitates.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in

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suitable proportions and compacted in the shape and size desired.

5 The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is
10 intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly,
15 cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

20 For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

25 Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol
30 solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

35 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component

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in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

5 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition
10 to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

15 The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as
20 packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

25 The quantity of active component in a unit dose preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

30 In therapeutic use as hypolipidemic and/or hypocholesterolemic agents, the crystalline Forms I, II, and Form IV atorvastatin utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 2.5 mg to
35 about 80 mg daily. A daily dose range of about 2.5 mg to about 20 mg is preferred. The dosages, however, may

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be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

Method A

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate (11.94 kg) dissolved in water (410 L), over at least

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30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to
5 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I
10 atorvastatin (72.2 kg).

Method B

Amorphous atorvastatin (9 g) and crystalline Form I atorvastatin (1 g) are stirred at about 40°C in
15 a mixture of water (170 mL) and methanol (30 mL) for a total of 17 hours. The mixture is filtered, rinsed with water, and dried at 70°C under reduced pressure to give crystalline Form I atorvastatin (9.7 g).

20

EXAMPLE 2

[R-(R*,R*)1-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form II Atorvastatin)]

25

A mixture of amorphous and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70°C under reduced pressure to give crystalline Form II
30 atorvastatin.

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EXAMPLE 3

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form IV Atorvastatin)

5 A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number
10 5,273,995)(12 kg), MTBE (50 kg), methanol (30 L) is reacted with an aqueous solution of sodium hydroxide (1.83 kg in 150 L) at 50-55°C for 30-45 minutes to form the ring-opened sodium salt. After cooling to 20-25°C, the organic layer is discarded and the aqueous layer is
15 again extracted with MTBE (37 kg). The organic layer is discarded and the aqueous solution of the sodium salt is heated to 70-80°C and the residual MTBE is removed by distillation. The solution is then cooled to 60-70°C. To this solution is added a solution of
20 calcium acetate hemihydrate (1.91 kg) dissolved in water/methanol (72 L water + 16 L methanol). The mixture is seeded with crystalline Form I atorvastatin (180 g) shortly after addition of the calcium acetate solution. The mixture is heated at 65-75°C for at
25 least 5 minutes and then cooled to 50-55°C. The mixture is filtered and slurried in methanol (about 200 L) at 55-65°C and then cooled to 25-30°C and filtered. The solid is dried at 66-70°C under vacuum to give Form IV of crystalline atorvastatin (about 3 kg
30 isolated).

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CLAIMS

1. Crystalline Form I atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >20% measured after 2 minutes of grinding using $\text{CuK}\alpha$ radiation:

	2θ	d	Relative Intensity (>20%) Ground 2 Minutes
	9.150	9.6565	42.60
	9.470	9.3311	41.94
	10.266	8.6098	55.67
	10.560	8.3705	29.33
15	11.853	7.4601	41.74
	12.195	7.2518	24.62
	17.075	5.1887	60.12
	19.485	4.5520	73.59
	21.626	4.1059	100.00
20	21.960	4.0442	49.44
	22.748	3.9059	45.85
	23.335	3.8088	44.72
	23.734	3.7457	63.04
	24.438	3.6394	21.10
25	28.915	3.0853	23.42
	29.234	3.0524	23.36

2. Crystalline Form I atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

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5	Assignment	Chemical
	(7 kHz)	Shift
	C12 or C25	182.8
	C12 or C25	178.4
	C16	166.7 (broad) and 159.3
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	137.0
		134.9
		131.1
		129.5
		127.6
15		123.5
		120.9
		118.2
		113.8
	C8,C10	73.1
20		70.5
		68.1
		64.9
	Methylene Carbons	
	C6, C7, C9, C11	47.4
25		41.9
		40.2
	C33	26.4
		25.2
	C34	21.3

3. Crystalline Form I atorvastatin of Claim 1 in which the hydrate is a trihydrate.
4. Crystalline Form II atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of

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5 the 2 θ , d-spacings, and relative intensities with
a relative intensity of >20% measured after
2 minutes of grinding using CuK α radiation:

	2 θ	d	Relative Intensity (>20%) Ground 2 Minutes
	5.582	15.8180	42.00
	7.384	11.9620	38.63
10	8.533	10.3534	100.00
	9.040	9.7741	92.06
	12.440 (broad)	7.1094	30.69
	15.771 (broad)	5.6146	38.78
	17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
15	19.490	4.5507	56.64
	20.502	4.3283	67.20
	22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
	25.697 (broad)	3.4639	38.93
	29.504	3.0250	37.86

5. Crystalline Form II atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

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5	Assignment	Chemical Shift
	Spinning Side Band	209.1
	Spinning Side Band	206.8
	C12 or C25	181 (broad)
	C12 or C25	163 (broad)
10	C16	161 (broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.5
		134.8
		133.3
15		129.0
		122.9
		121.4
		120.3
		119.0
20		117.1
		115.7
		114.7
	C8, C10	70.6
		69.0
25		68.0
		67.3
	Spinning Side Band	49.4
	Spinning Side Band	48.9
	Methylene Carbons	
30	C6, C7, C9, C11	43.4
		42.3
		41.7
		40.2
	C33	27.5
35	C34	22.8 (broad)

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6. Crystalline Form IV atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >15% measured using $\text{CuK}\alpha$ radiation:

5

	2θ	d	Relative Intensity (>15%)
	4.889	18.605	38.45
10	5.424	16.2804	20.12
	5.940	14.8660	17.29
	7.997	11.0465	100.00
	9.680	9.1295	67.31
	10.416	8.4859	20.00
15	12.355	7.1584	19.15
	17.662	5.0175	18.57
	18.367	4.8265	23.50
	19.200	4.6189	18.14
	19.569	4.5327	54.79
20	21.723	4.0879	17.99
	23.021	3.8602	28.89
	23.651	3.7587	33.39
	24.143	3.6832	17.23

7. Crystalline Form IV atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million:

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	Assignment	Chemical Shift
5	C12 or C25	186.4
		184.9
	C12 or C25	181.4
		179.3
	C16	166.1 (broad) and 159.0 (broad)
	Aromatic Carbons	
10	C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
		134.7
		129.2
		127.1
		122.7
		119.8
		115.7
	C8, C10	71.5
		67.9
		66.3
		63.5
	Methylene Carbons	
15	C6, C7, C9, C11	46.1
		43.4
		42.1
		40.0
	C33	25.9
	C34	20.3
		19.4
		17.9

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8. A pharmaceutical composition in the form of tablets comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one pharmaceutically acceptable excipient,
5 diluent, or carrier.
9. A pharmaceutical composition in the form of capsules comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically
5 acceptable excipient, diluent, or carrier.
10. A pharmaceutical composition in the form of a powder comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient,
5 diluent, or carrier.
11. A pharmaceutical composition in the form of lozenges comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically
5 acceptable excipient, diluent, or carrier.
12. A pharmaceutical composition in the form of suppositories comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically
5 acceptable excipient, diluent, or carrier.
13. A pharmaceutical composition in the form of retention enemas comprising crystalline Form I atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically
5 acceptable excipient, diluent, or carrier.

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14. A method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
15. A process for the preparation of crystalline Form I atorvastatin comprising:
Step (a) treating an aqueous solution of a basic salt of [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid with a calcium salt; and
Step (b) isolating crystalline Form I atorvastatin.
16. A process according to Claim 15 wherein in Step (a) seeds of crystalline Form I atorvastatin are added during or after treating the aqueous solution of a basic salt of [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid with a calcium salt.
17. A process according to Claim 15 wherein in Step (a) the aqueous solution contains a hydroxylic co-solvent and methyl tert-butyl ether.
18. A process according to Claim 17 wherein in Step (a) the hydroxylic co-solvent is methanol.
19. A process according to Claim 15 wherein in Step (a) the calcium salt is calcium acetate.

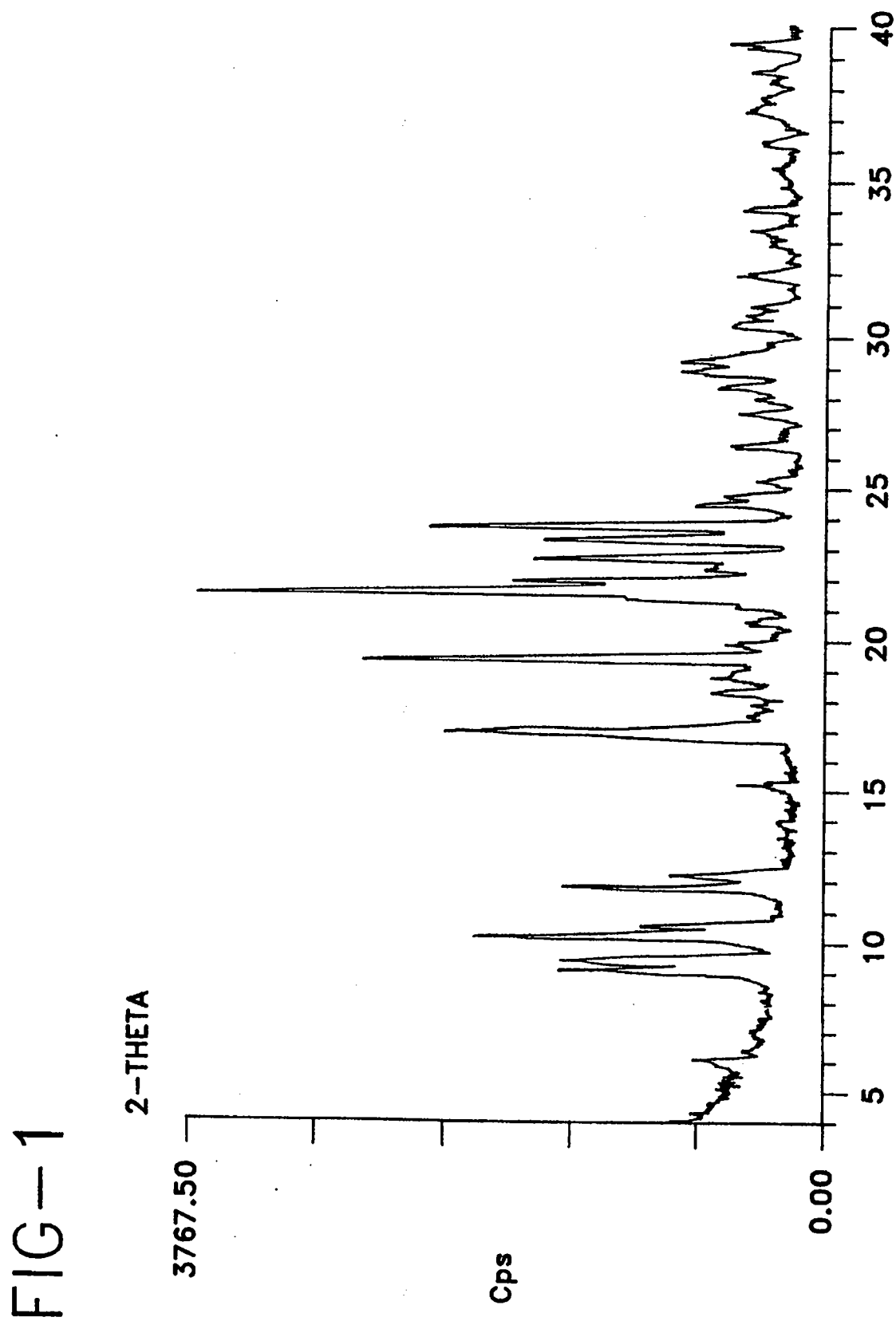
-37-

20. A process according to Claim 15 wherein in Step (b) crystalline Form I atorvastatin is further dried.
21. A process according to Claim 20 wherein in Step (b) crystalline Form I atorvastatin is further dried under reduced pressure.
22. A process according to Claim 15 wherein in Step (a) the basic salt is selected from the group consisting of an alkali metal salt, ammonia, and an amine salt.
23. A process according to Claim 22 wherein in Step (a) the basic salt is the sodium salt.
24. A process according to Claim 15 wherein two moles of the basic salt to one mole of the calcium salt is used.
25. A process for the preparation of crystalline Form I atorvastatin comprising:
Step (a) suspending a mixture of amorphous atorvastatin and crystalline Form I atorvastatin in water containing a co-solvent; and
Step (b) isolating crystalline Form I atorvastatin.
26. A process according to Claim 25 wherein in Step (a) the co-solvent is selected from the group consisting of methanol, ethanol, 2-propanol, and acetone.
27. A process according to Claim 26 wherein in Step (a) the co-solvent is methanol.

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28. A process according to Claim 25 wherein in Step (b) crystalline Form I atorvastatin is further dried.
29. A process according to Claim 28 wherein in Step (b) crystalline Form I atorvastatin is further dried under reduced pressure.

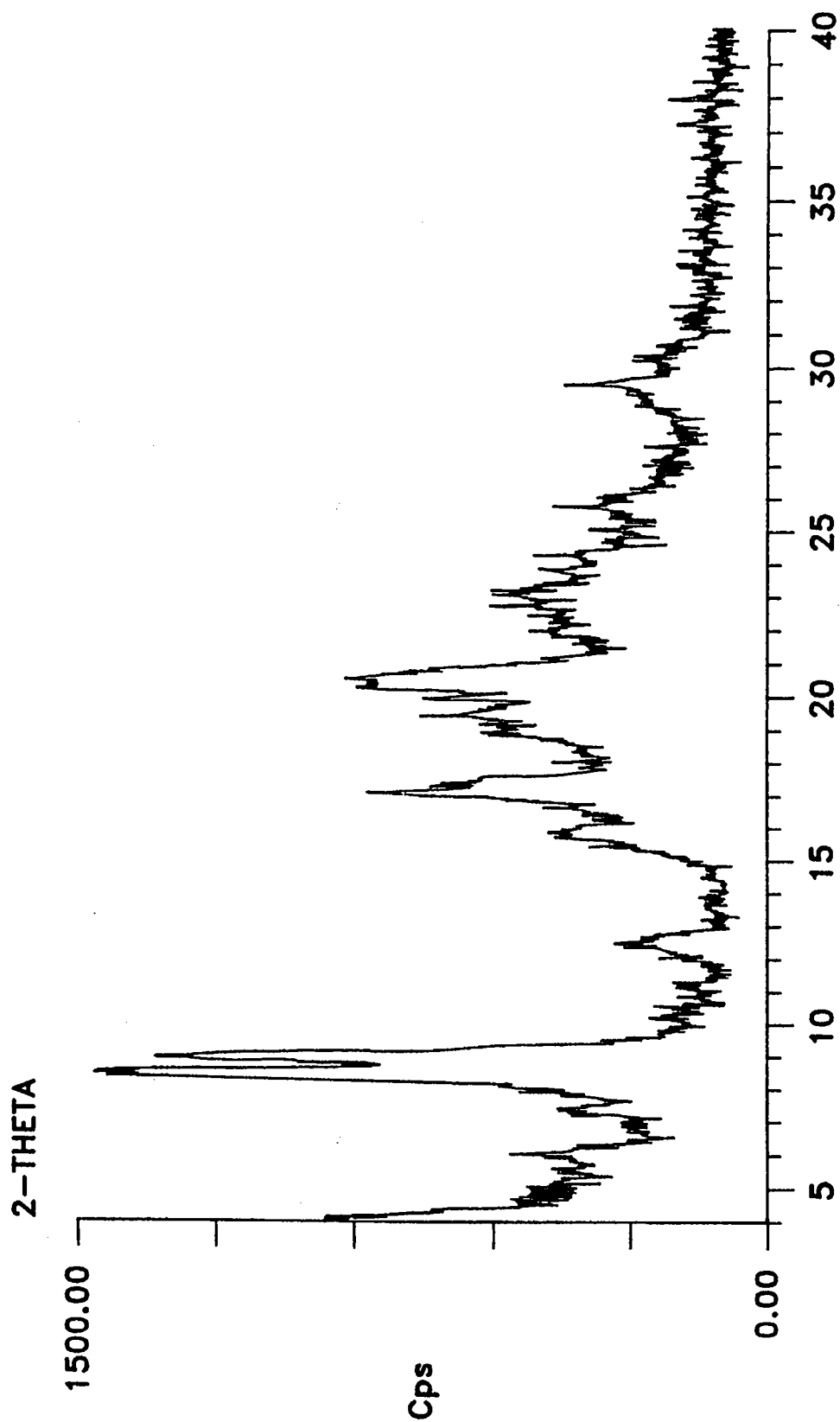
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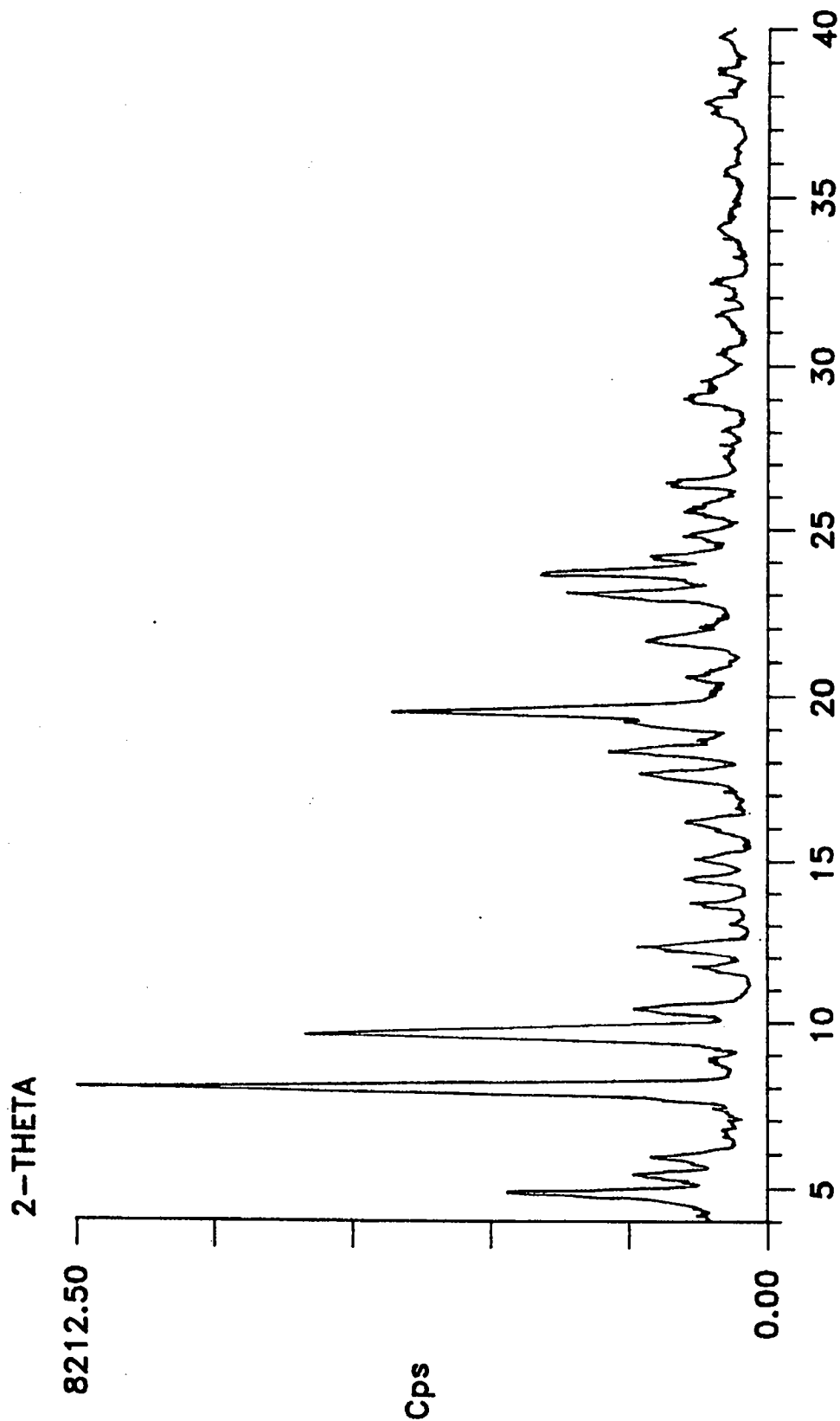
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FIG-2



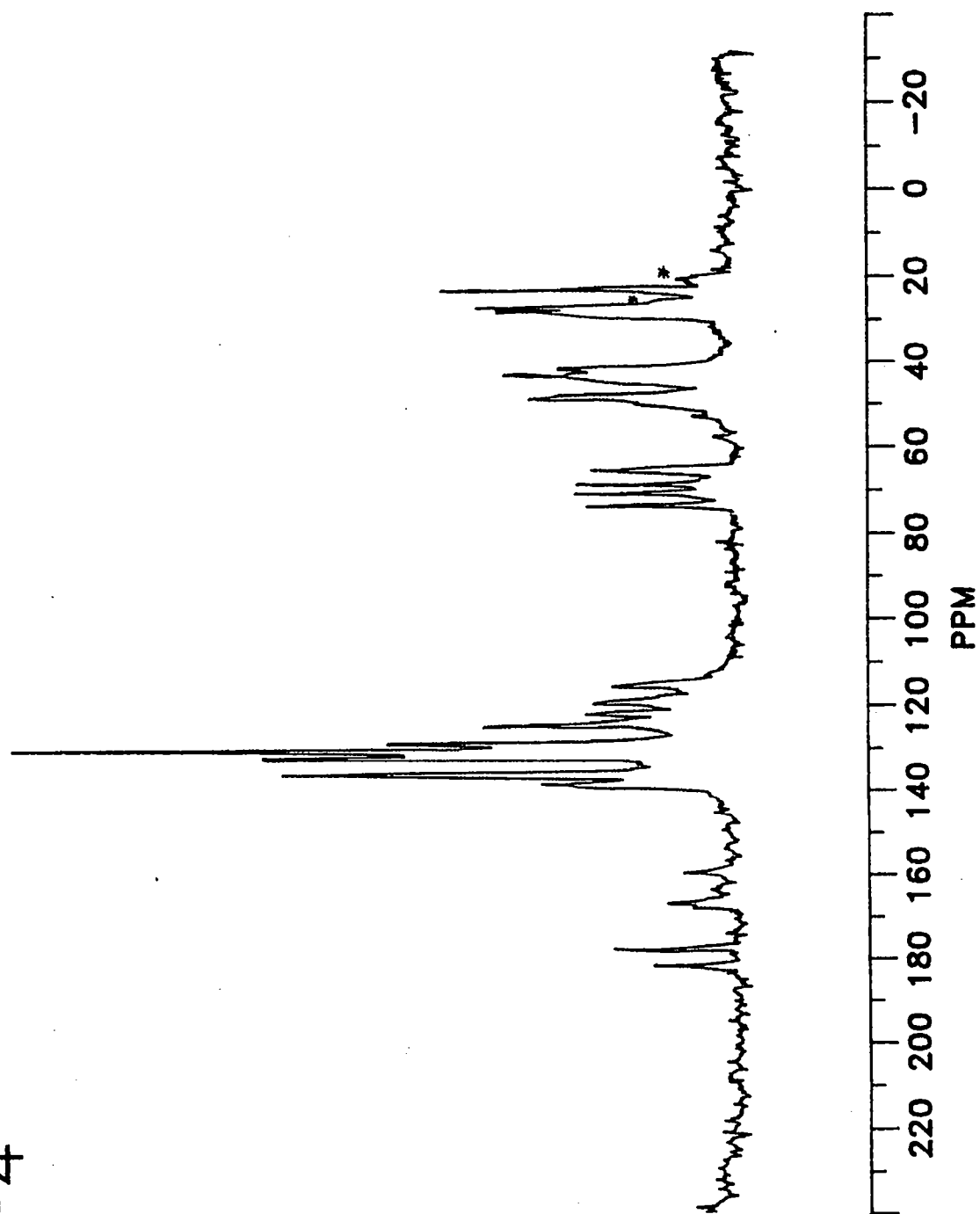
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FIG-3

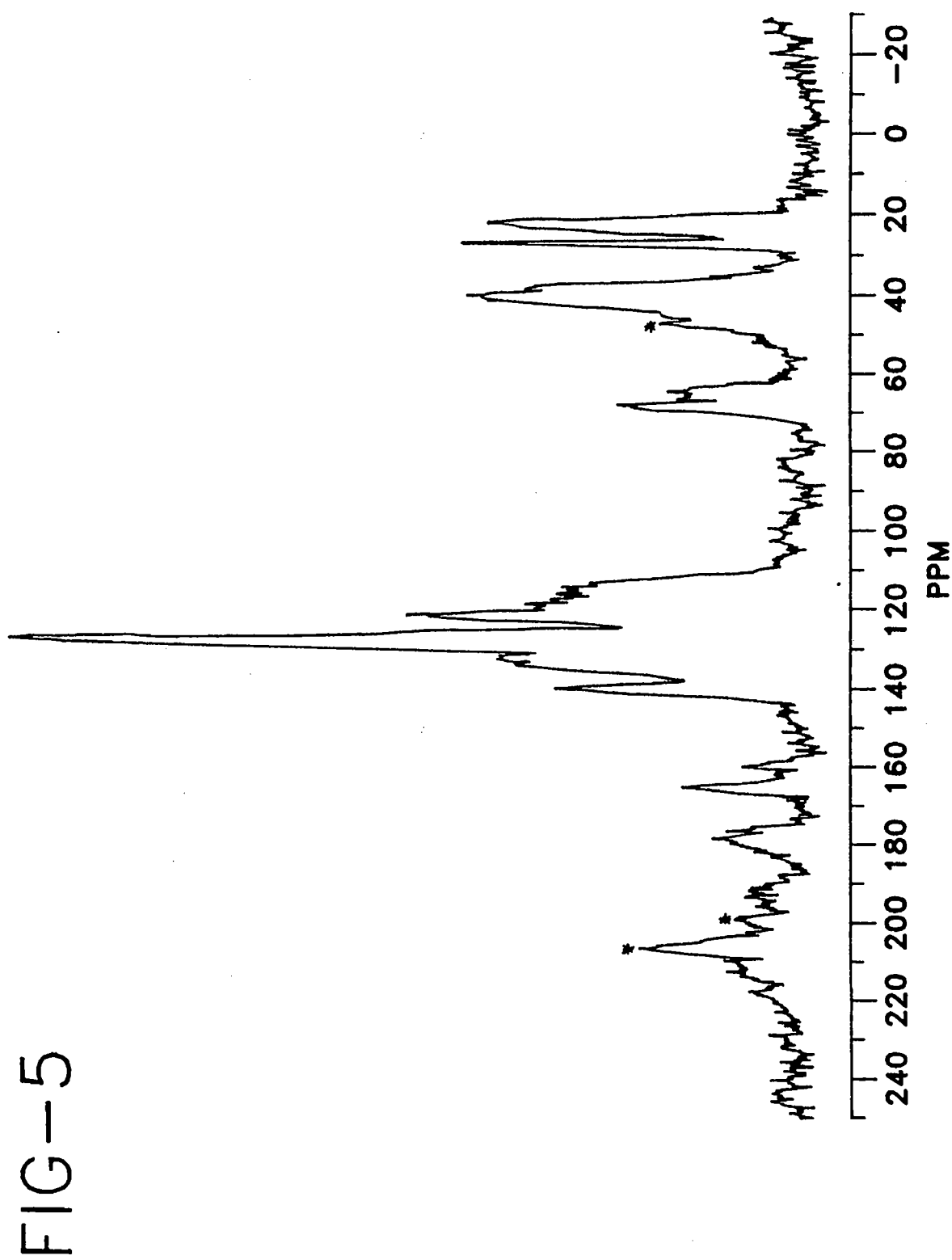


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FIG-4

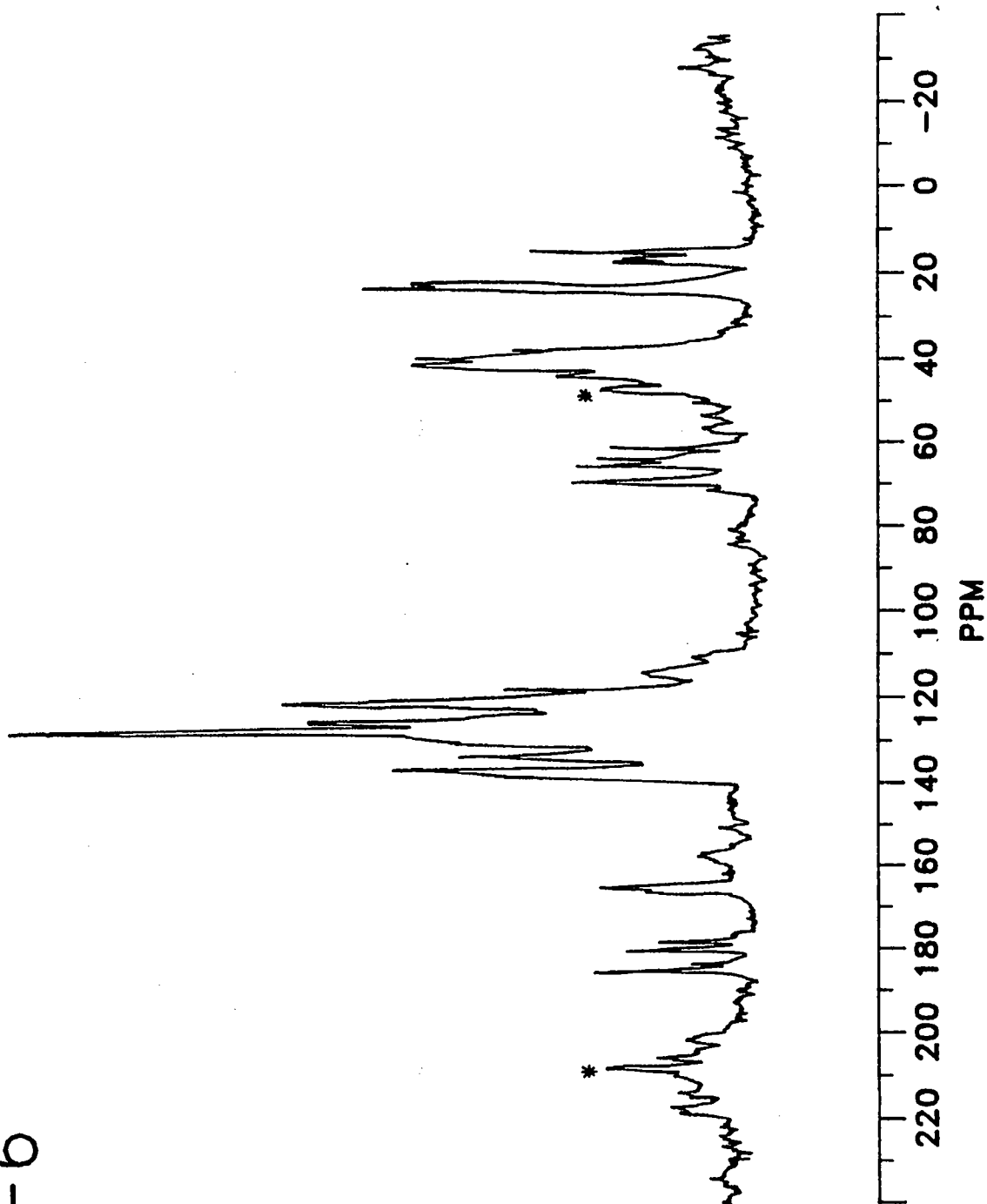


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FIG-6



INTERNATIONAL SEARCH REPORT

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International Application No
PC1/US 96/11368

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/34 A61K31/40

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

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IPC 6 C07D

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 16693 A (WARNER-LAMBERT CO., USA) 4 August 1994 see the whole document ---	1-29
A	US 5 316 765 A (FOLKERS, KARL A. ET AL) 31 May 1994 see the whole document ---	1-29
A	TETRAHEDRON LETT. (1992), 33(17), 2283-4 CODEN: TELEAY;ISSN: 0040-4039, 1992, XP000608147 BAUMANN, KELVIN L. ET AL: "The convergent synthesis of CI-981, an optically active, highly potent, tissue-selective inhibitor of HMG-CoA reductase" see the whole document --- -/--	1-29

☒ Further documents are listed in the continuation of box C.

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 409 281 A (WARNER-LAMBERT CO., USA) 23 January 1991 see the whole document -----	1-29

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US96/11367 (22) International Filing Date: 8 July 1996 (08.07.96) (30) Priority Data: 60/001,454 17 July 1995 (17.07.95) US (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): MCKENZIE, Ann, T. [US/US]; 1932 Happy Hollow Road, West Lafayette, IN 47906 (US). (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.		(81) Designated States: AU, BG, BR, CA, CN, CZ, EE, GE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, UZ, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: FORM III CRYSTALLINE (R-(R*,R*))·2-(4-FLUOROPHENYL)-BETA-DELTA-DIHYDROXY-5-(1-METHYL-ETHYL)-3-PHENYL-4-((PHENYLAMINO)CARBONYL)-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN) (57) Abstract A novel crystalline form of [R-(R*,R*)]·2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt designated Form III is characterized by its X-ray powder diffraction and/or solid state NMR is described, as well as methods for the preparation and pharmaceutical composition of the same, which is useful as an agent for treating hyperlipidemia and hypercholesterolemia.		

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5 FORM III CRYSTALLINE (R-(R*,R*)-2-(4-FLUOROPHENYL)-BETA-DELTA-DIHYDROXY-5-(1-METHYL-ETHYL)-3-PHENYL-4-((PHENYLAMINO)CARBONYL)-1H-PYRROLE-1-HEPTANOIC ACID HEMI CALCIUM SALT (ATORVASTATIN)

10

BACKGROUND OF THE INVENTION

The present invention relates to a novel crystalline form of atorvastatin which is known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -
15 dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt useful as a pharmaceutical agent, to methods for its production and isolation, to pharmaceutical compositions which include this compound and a
20 pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel crystalline compound of the present invention is useful as an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase)
25 and is thus useful as a hypolipidemic and hypocholesterolemic agent.

United States Patent Number 4,681,893, which is herein incorporated by reference, discloses certain
30 trans-6-[2-(3- or 4-carboxamido-substituted-pyrrol-1-yl)alkyl]-4-hydroxy-pyran-2-ones including trans ($\pm$)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

United States Patent Number 5,273,995, which is
35 herein incorporated by reference, discloses the enantiomer having the R form of the ring-opened acid of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[(2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide, i.e.,

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[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid.

United States Patent Numbers 5,003,080; 5,097,045;
5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174;
5,245,047; 5,248,793; 5,280,126; 5,397,792; and
5,342,952, which are herein incorporated by reference,
disclose various processes and key intermediates for
preparing atorvastatin.

Atorvastatin is prepared as its calcium salt,
i.e., [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The
calcium salt is desirable since it enables atorvastatin
to be conveniently formulated in, for example, tablets,
capsules, lozenges, powders, and the like for oral
administration. Additionally, there is a need to
produce atorvastatin in a pure and crystalline form to
enable formulations to meet exacting pharmaceutical
requirements and specifications.

Furthermore, the process by which atorvastatin is
produced needs to be one which is amenable to large-
scale production. Additionally, it is desirable that
the product should be in a form that is readily
filterable and easily dried. Finally, it is
economically desirable that the product be stable for
extended periods of time without the need for
specialized storage conditions.

The processes in the above United States Patents
disclose amorphous atorvastatin which has unsuitable
filtration and drying characteristics for large-scale
production and must be protected from heat, light,
oxygen, and moisture.

We have now surprisingly and unexpectedly found
that atorvastatin can be prepared in crystalline form.
Thus, the present invention provides atorvastatin in a

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new crystalline form designated Form III. Form III atorvastatin has different physical characteristics compared to the previous amorphous product.

5

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to crystalline Form III atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >25% measured on a Siemens D-500 diffractometer with $\text{CuK}\alpha$ radiation:

15

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	2 θ	d	Relative Intensity (>25%)
	4.123	21.4140	49.20
	4.993	17.6832	30.82
	5.768	15.3099	28.69
5	7.670	11.5173	25.49
	8.451	10.4538	100.00
	15.962	5.5478	32.59
	16.619	5.3298	62.34
	17.731	4.9981	49.29
10	18.267	4.8526	45.12
	18.870	4.6989	39.52
	19.480	4.5531	36.59
	19.984	4.4393	70.34
	20.294	4.3722	69.54
15	21.105	4.2061	37.39
	21.670	4.0976	36.50
	23.318	3.8117	38.63
	24.405	3.6442	65.54
	24.967	3.5635	27.20
20	25.397	3.5041	33.75

Further, the present invention is directed to crystalline Form III atorvastatin and hydrates thereof characterized by the following solid-state ^{13}C nuclear magnetic resonance spectrum wherein chemical shift is expressed in parts per million measured on a Bruker AX-250 spectrometer:

30

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		Assignment	Chemical Shift
		Spinning Side Band	214.8
			209.3
			202.3
5		C12 or C25	184.9
		C12 or C25	166.7
		C16	161.0(weak, broad)
		Aromatic Carbons	
		C2-C5, C13-C18, C19-C24, C27-C32	140.1
10			135.2
			131.8
			128.9
			124.3
			122.2
15			117.2
			114.9
		C8, C10	69.8
			67.3
			65.6
20		Methylene Carbons	
		C6, C7, C9, C11	44.1
			40.4
			35.4
		C33	27.0
25			24.1
		C34	22.1
			19.9

30 As an inhibitor of HMG-CoA, the novel crystalline form of atorvastatin is useful as a hypolipidemic and hypocholesterolemic agent.

A still further embodiment of the present invention is a pharmaceutical composition for

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administering an effective amount of crystalline
Form III atorvastatin in unit dosage form in the
treatment methods mentioned above. Finally, the
present invention is directed to methods for production
5 of Form III atorvastatin.

BRIEF DESCRIPTION OF THE DRAWINGS

10 The invention is further described by the
following nonlimiting examples which refer to the
accompanying Figures 1 to 2, short particulars of which
are given below.

15 Figure 1

Diffractiongram of Form III atorvastatin (Y-axis = 0
to maximum intensity of 2815 counts per seconds (cps)).

Figure 2

20 Solid-state ^{13}C nuclear magnetic resonance
spectrum with spinning side bands identified by an
asterisk of Form III atorvastatin.

25 DETAILED DESCRIPTION OF THE INVENTION

Crystalline Form III atorvastatin may be
characterized by its X-ray powder diffraction pattern
and/or by its solid state nuclear magnetic resonance
30 spectra (NMR).

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X-RAY POWDER DIFFRACTION

Form III Atorvastatin

5 Form III atorvastatin was characterized by its X-ray powder diffraction pattern. Thus, the X-ray diffraction pattern of Form III atorvastatin was measured on a Siemens D-500 diffractometer with CuK_α radiation.

10 Equipment

Siemens D-500 Diffractometer-Kristalloflex with an IBM-compatible interface, software = DIFFRAC AT (SOCABIM 1986, 1992).

15 CuK_α radiation (20 mA, 40 kV, $\lambda = 1.5406 \text{ \AA}$) Slits I and II at 1° electronically filtered by the Kevex Psi Peltier Cooled Silicon [Si(Li)] Detector (Slits: III at 1° and IV at 0.15°).

Methodology

20 The silicon standard is run each day to check the X-ray tube alignment.

Continuous $\theta/2\theta$ coupled scan: 4.00° to 40.00° in 2θ , scan rate of $6^\circ/\text{min}$: 0.4 sec/ 0.04° step.

25 Sample tapped out of vial and pressed onto zero-background quartz in Al holder. Sample width 13-15 mm.

Samples are stored and run at room temperature.

30 Table 1 lists the 2θ , d-spacings, and relative intensities of all lines in the unground sample with a relative intensity of $>25\%$ for crystalline Form III atorvastatin. It should also be noted that the computer-generated unrounded numbers are listed in this table.

35

TABLE 1. Intensities and Peak Locations of All Diffraction Lines With Relative Intensity Greater Than 25% for Form III Atorvastatin

	2θ	d	Relative Intensity (>25%)
5	4.123	21.4140	49.20
	4.993	17.6832	30.82
	5.768	15.3099	28.69
	7.670	11.5173	25.49
10	8.451	10.4538	100.00
	15.962	5.5478	32.59
	16.619	5.3298	62.34
	17.731	4.9981	49.29
	18.267	4.8526	45.12
15	18.870	4.6989	39.52
	19.480	4.5531	36.59
	19.984	4.4393	70.34
	20.294	4.3722	69.54
	21.105	4.2061	37.39
20	21.670	4.0976	36.50
	23.318	3.8117	38.63
	24.405	3.6442	65.54
	24.967	3.5635	27.20
	25.397	3.5041	33.75

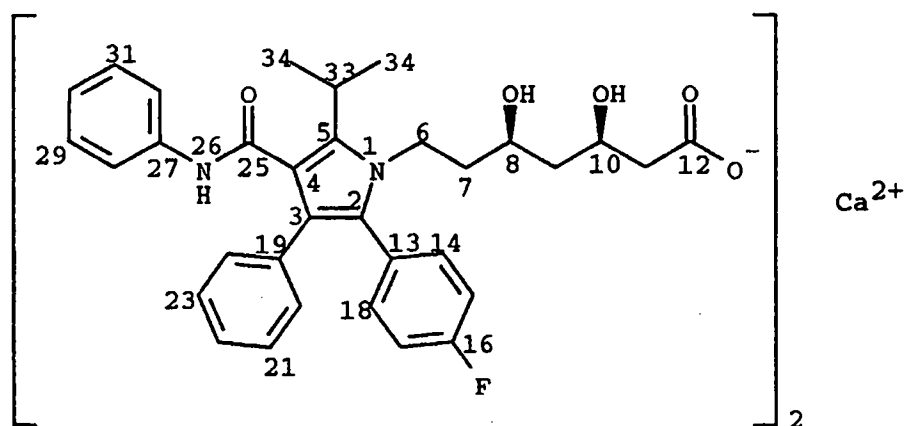
SOLID STATE NUCLEAR MAGNETIC RESONANCE (NMR)

Methodology

30 All solid-state ¹³C NMR measurements were made with a Bruker AX-250, 250 MHz NMR spectrometer. High resolution spectra were obtained using high-power proton decoupling and cross-polarization (CP) with magic-angle spinning (MAS) at approximately 5 kHz. The
35 magic-angle was adjusted using the Br signal of KBr by

detecting the side bands as described by Frye and Maciel (Frye J.S. and Maciel G.E., J. Mag. Res., 1982;48:125). Approximately 300 to 450 mg of sample packed into a canister-design rotor was used for each experiment. Chemical shifts were referenced to external tetrakis (trimethylsilyl)silane (methyl signal at 3.50 ppm) (Muntean J.V. and Stock L.M., J. Mag. Res., 1988;76:54).

Table 2 shows the solid-state NMR spectrum for crystalline Form III atorvastatin.



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TABLE 2. Carbon Atom Assignment and Chemical Shift for Form III Atorvastatin

Assignment		Chemical Shift
5	Spinning Side Band	214.8
		209.3
		202.3
	C12 or C25	184.9
	C12 or C25	166.7
10	C16	161.0 (weak, broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.1
		135.2
		131.8
15		128.9
		124.3
		122.2
		117.2
		114.9
20	C8, C10	69.8
		67.3
		65.6
	Methylene Carbons	
	C6, C7, C9, C11	44.1
25		40.4
		35.4
	C33	27.0
		24.1
	C34	22.1
30		19.9

Crystalline Form III atorvastatin of the present invention can exist in anhydrous form as well as hydrated forms. In general, the hydrated forms, are equivalent to unhydrated forms and are intended to be

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encompassed within the scope of the present invention.

The present invention also provides a process for the preparation of crystalline Form III atorvastatin which comprises exposing atorvastatin to a high
5 relative humidity under conditions which yield crystalline Form III atorvastatin.

The precise conditions under which Form III of crystalline atorvastatin is formed may be empirically determined and it is only possible to give a method
10 which has been found to be suitable in practice.

Thus, for example, when the starting material is Form II of crystalline atorvastatin disclosed in concurrently filed United States Patent Application titled "Crystalline [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -
15 dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1)" commonly owned, attorney's Case Number PD-5250-01-FJT, Serial Number _____ (Crystalline Form I and Form IV atorvastatin are also disclosed in this
20 application), the desired Form III of crystalline atorvastatin may be obtained by exposing the solid to a relative humidity of 95% for 11 days.

Crystalline Form II atorvastatin may be prepared from amorphous, a combination of amorphous and
25 crystalline Form I atorvastatin or crystalline Form I atorvastatin. Thus, for example, when the starting material is amorphous, a combination of amorphous and Form I, or crystalline Form I atorvastatin, the desired Form II of crystalline atorvastatin may be obtained by
30 suspending the solid in methanol containing about 40% to about 50% water until conversion to the required form is complete, followed by filtration.

Crystalline Form I atorvastatin may be prepared by crystallization under controlled conditions. In
35 particular, it can be prepared either from an aqueous solution of the corresponding basic salt such as, an

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alkali metal salt, for example, lithium, potassium, sodium, and the like; ammonia or an amine salt; preferably, the sodium salt by addition of a calcium salt, such as, for example, calcium acetate and the like, or by suspending amorphous atorvastatin in water. In general, the use of a hydroxylic co-solvent such as, for example, a lower alkanol, for example methanol and the like, is preferred.

The compound of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compound of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compound of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compound of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either compounds or a corresponding pharmaceutically acceptable salt of the compound of the present invention.

For preparing pharmaceutical compositions from the compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

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In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

5 The powders and tablets preferably contain from two or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, 10 sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with 15 or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

20 For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into 25 convenient sized molds, allowed to cool, and thereby to solidify.

 Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example water or water propylene glycol solutions. For 30 parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, 35 and thickening agents as desired.

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Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents..

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.5 mg to 100 mg, preferably 2.5 mg to 80 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as a hypolipidemic and/or hypocholesterolemic agent, crystalline Form III atorvastatin utilized in the pharmaceutical method of this invention is administered at the initial dosage of about 2.5 mg to about 80 mg daily. A daily dose range

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of about 2.5 mg to about 20 mg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstance is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

EXAMPLE 1

[R-(R*,R*)]-2-(4-Fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form I Atorvastatin)

A mixture of (2R-trans)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (atorvastatin lactone) (United States Patent Number 5,273,995) (75 kg), methyl tertiary-butyl ether (MTBE) (308 kg), methanol (190 L) is reacted with an aqueous solution of sodium hydroxide (5.72 kg in 950 L) at 48-58°C for 40 to 60 minutes to form the ring-opened sodium salt. After cooling to 25-35°C, the organic layer is discarded, and the aqueous layer is again extracted with MTBE (230 kg). The organic layer is discarded, and the MTBE saturated aqueous solution of the sodium salt is heated to 47-52°C. To this solution is added a solution of calcium acetate hemihydrate

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(11.94 kg) dissolved in water (410 L), over at least 30 minutes. The mixture is seeded with a slurry of crystalline Form I atorvastatin (1.1 kg in 11 L water and 5 L methanol) shortly after addition of the calcium acetate solution. The mixture is then heated to 51-57°C for at least 10 minutes and then cooled to 15-40°C. The mixture is filtered, washed with a solution of water (300 L) and methanol (150 L) followed by water (450 L). The solid is dried at 60-70°C under vacuum for 3 to 4 days to give crystalline Form I atorvastatin (72.2 kg).

EXAMPLE 2

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form II Atorvastatin)

A mixture of amorphous and crystalline Form I atorvastatin (100 g) was suspended in a mixture of methanol (1200 mL) and water (800 mL) and stirred for 3 days. The material was filtered, dried at 70°C under reduced pressure to give crystalline Form II atorvastatin.

EXAMPLE 3

[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt (Form III Atorvastatin)

Form II atorvastatin (Example 2) is rotapped through a 50 mesh screen onto a 100 mesh screen and exposed in a humidity jar to 95% relative humidity for 11 days to afford crystalline Form III atorvastatin.

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CLAIMS

1. Crystalline Form III atorvastatin and hydrates thereof characterized by the following X-ray powder diffraction pattern expressed in terms of the 2θ , d-spacings, and relative intensities with a relative intensity of >25% measured using $\text{CuK}\alpha$ radiation:

5

10

15

20

25

2θ	d	Relative Intensity (>25%)
4.123	21.4140	49.20
4.993	17.6832	30.82
5.768	15.3099	28.69
7.670	11.5173	25.49
8.451	10.4538	100.00
15.962	5.5478	32.59
16.619	5.3298	62.34
17.731	4.9981	49.29
18.267	4.8526	45.12
18.870	4.6989	39.52
19.480	4.5531	36.59
19.984	4.4393	70.34
20.294	4.3722	69.54
21.105	4.2061	37.39
21.670	4.0976	36.50
23.318	3.8117	38.63
24.405	3.6442	65.54
24.967	3.5635	27.20
25.397	3.5041	33.75

2. Crystalline Form III atorvastatin and hydrates thereof characterized by the following solid-state

-18-

¹³C nuclear magnetic resonance spectrum wherein
chemical shift is expressed in parts per million:

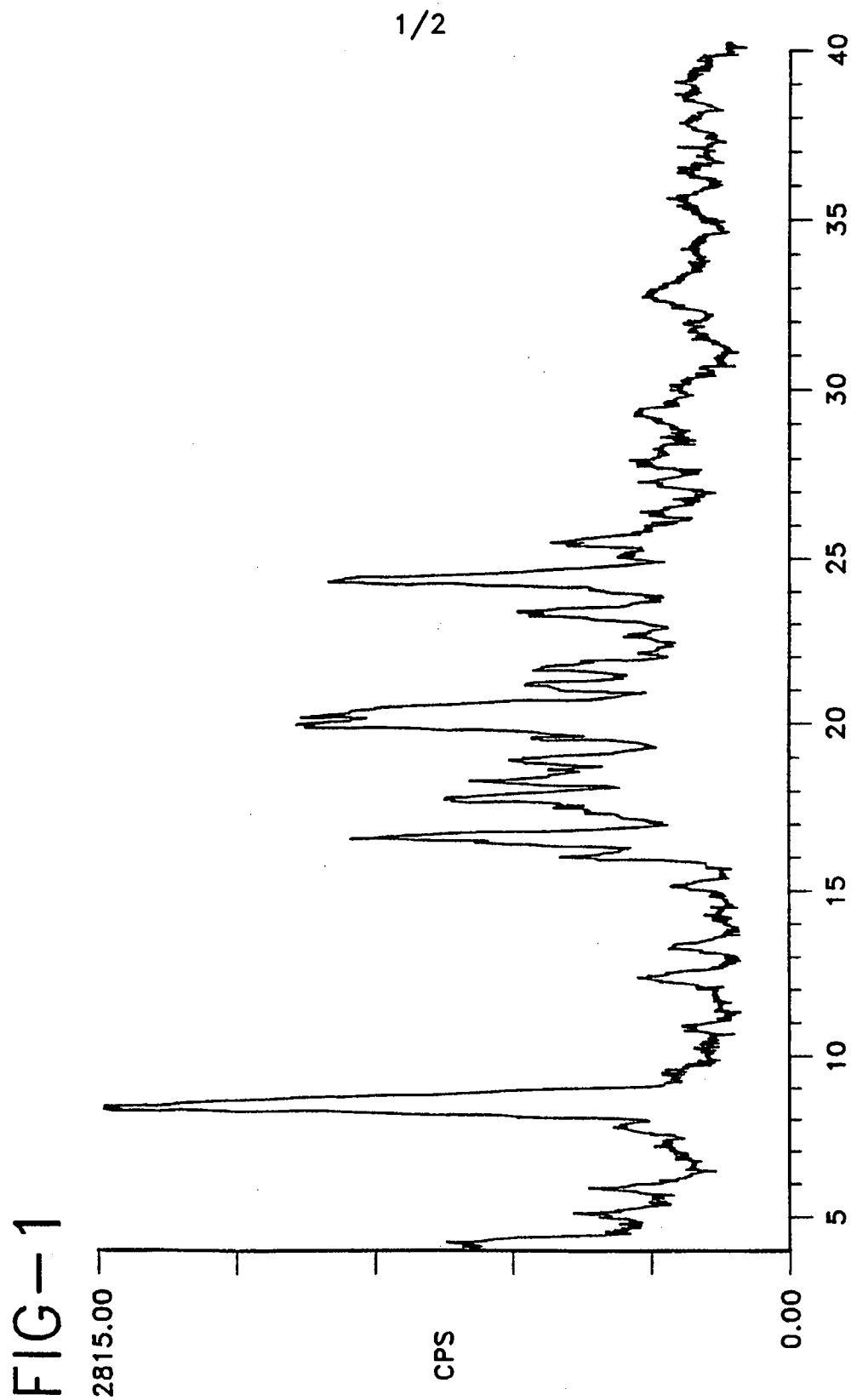
5	Assignment	Chemical Shift
	Spinning Side Band	214.8
		209.3
		202.3
	C12 or C25	184.9
10	C12 or C25	166.7
	C16	161.0 (weak, broad)
	Aromatic Carbons	
	C2-C5, C13-C18, C19-C24, C27-C32	140.1
		135.2
15		131.8
		128.9
		124.3
		122.2
		117.2
20		114.9
	C8, C10	69.8
		67.3
		65.6
	Methylene Carbons	
25	C6, C7, C9, C11	44.1
		40.4
		35.4
	C33	27.0
		24.1
30	C34	22.1
		19.9

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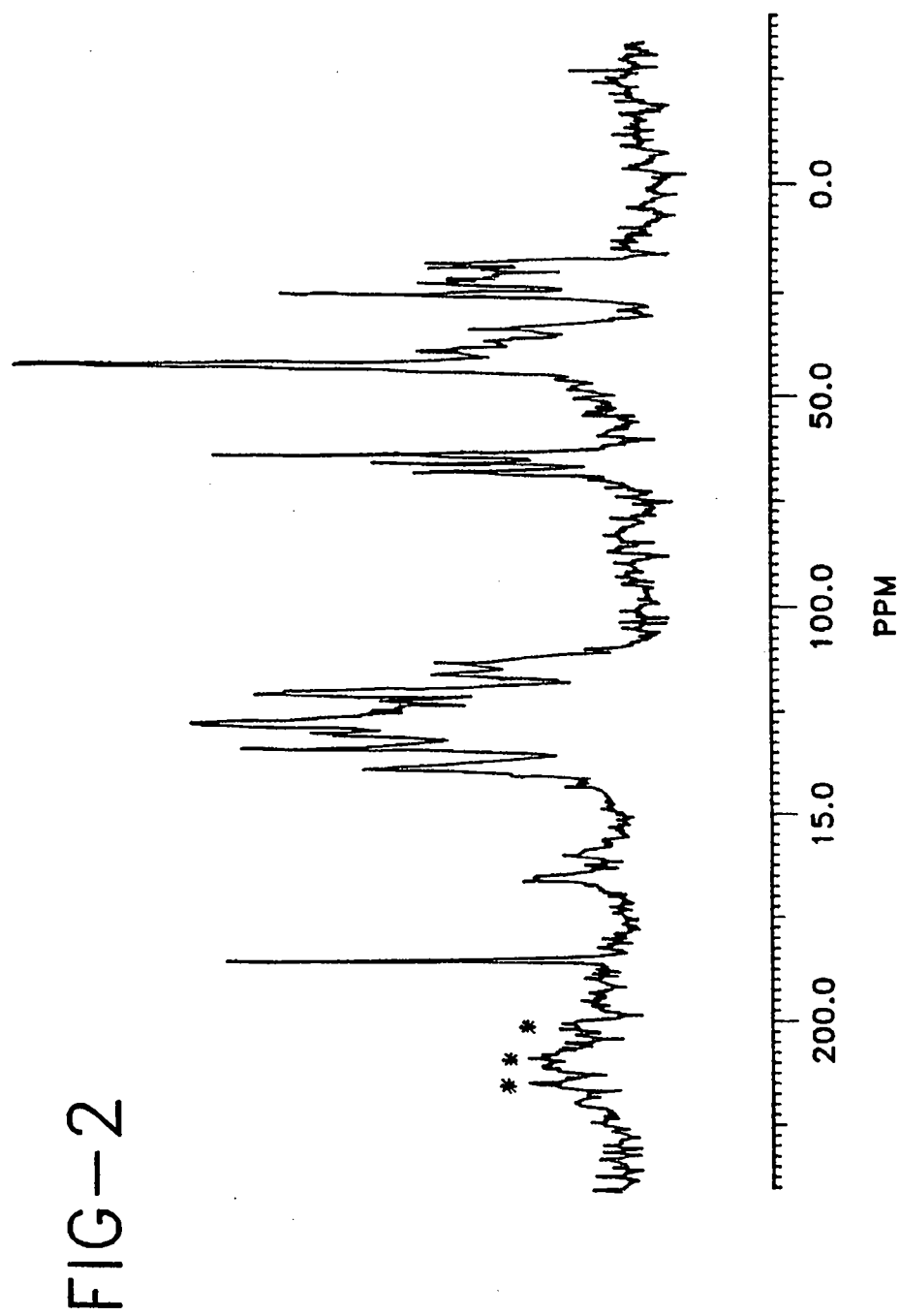
3. A pharmaceutical composition in the form of tablets comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one pharmaceutically acceptable excipient, diluent, or carrier.
5
4. A pharmaceutical composition in the form of capsules comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
5. A pharmaceutical composition in the form of a powder comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
6. A pharmaceutical composition in the form of lozenges comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
7. A pharmaceutical composition in the form of suppositories comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5
8. A pharmaceutical composition in the form of retention enemas comprising crystalline Form III atorvastatin as defined in Claim 1 in admixture with at least one inert pharmaceutically acceptable excipient, diluent, or carrier.
5

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9. A method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to Claim 1 in unit dosage form.
- 5



2/2



INTERNATIONAL SEARCH REPORT

517

Int'l Application No PCT/US 96/11367		
A. CLASSIFICATION OF SUBJECT MATTER IPC 6 C07D207/34 A61K31/40		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C07D		
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 practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 16693 A (WARNER-LAMBERT CO., USA) 4 August 1994 see the whole document ---	1-9
A	US 5 316 765 A (FOLKERS, KARL A. ET AL) 31 May 1994 see the whole document ---	1-9
A	TETRAHEDRON LETT. (1992), 33(17), 2283-4 CODEN: TELEAY; ISSN: 0040-4039, 1992, XP000608147 BAUMANN, KELVIN L. ET AL: "The convergent synthesis of CI-981, an optically active, highly potent, tissue-selective inhibitor of HMG-CoA reductase" see the whole document --- -/--	1-9
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "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) "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 "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 "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 "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 * & document member of the same patent family		
Date of the actual completion of the international search 21 October 1996		Date of mailing of the international search report 25.10.96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016		Authorized officer Kissler, B

INTERNATIONAL SEARCH REPORT

518

Int'l Application No
PCT/US 96/11367

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 409 281 A (WARNER-LAMBERT CO., USA) 23 January 1991 see the whole document -----	1-9

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES**

202075

Bogotá, D.C., (28 de Junio del 2007)

Abogado

CARLOS R. OLARTE.

(Apoderado)

Solicitante: Warner – Lambert Company LLC

ASUNTO	Radicación	03107810
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	83

... 000-8528

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 76 a 156 como se radicó inicialmente

1.2. Reivindicaciones: Folios 157 a 161 como se radicó inicialmente

1.3. Dibujos: Folios 163 a 197 como se radicó inicialmente

1.4. Oposiciones: Procaps S.A.

Folios 206 'a 324

Tecnoquímicas S.A y Lafrancol S.A.

Folios 325 a 435

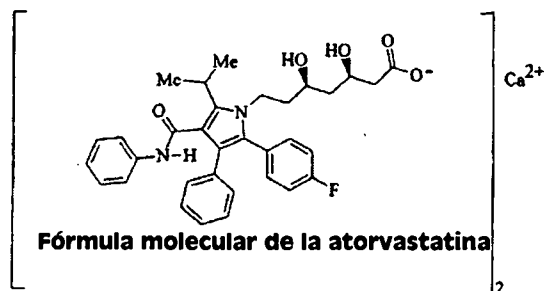
1.5. Prioridad: Folios 9 a 75 (29 de Junio de 2001, US, 60/302049).

2. Objeto de la invención

- Título de la solicitud: FORMAS CRISTALINAS DE LA SAL DE CALCIO DEL ÁCIDO [R-(R*, R*)]-2-(4-FLUOROFENIL)-β, δ-DIHIDROXI-5-(1-METILETIL)-3-FENIL-4-[(FENILAMINO)CARBONIL]-1H-PIRROL-1-HEPTANOICO (2:1).

El objeto de la presente solicitud de patente de invención consiste en nuevas formas cristalinas de la sal hemicálcica del ácido [R-(R*, R*)]-2-(4-fluorofenil)-β, δ-dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico, denominadas forma V, forma VI, forma VII, forma VIII, forma IX, forma X, forma XI, forma XII, forma XIII, forma XIV, forma XV, forma XVI, forma XVII, forma XVIII y forma XIX o un hidrato de las mismas.

Reivindicaciones 1-15 : Formas cristalinas de atorvastatina o un hidrato de la misma caracterizadas por su patrón de difracción de rayos X en polvo.



El problema planteado en esta solicitud es la necesidad de formas cristalinas de atorvastatina, que garanticen una mejor estabilidad química, que se puedan preparar en solventes menos tóxicos, una mejor propiedad para el tableteo, una vida media aumentada y fecha de caducidad posterior.

Para solucionar este problema técnico la solicitud en estudio proporciona formas cristalinas de atorvastatina, denominadas forma V, forma VI, forma VII, forma VIII, forma IX, forma X, forma XI, forma XII, forma XIII, forma XIV, forma XV, forma XVI, forma XVII, forma XVIII y forma XIX o un hidrato de las mismas, procedimientos para su preparación, composiciones farmacéuticas del mismo y métodos para utilizarlos.

El objeto de la invención definido anteriormente se clasifica de acuerdo con la Clasificación Internacional de Patentes (IPC) : A61K31/40, C07D207/34.

3. Análisis de la(s) Oposición(es): (artículo 43 D. 486):

3.1. Argumentos opositor Procaps S.A.

El opositor expone lo siguiente:

“ La molécula de atorvastatina antes de la fecha de prioridad de la solicitud en estudio, ya era parte del estado de la técnica. Se revelan los siguientes documentos en los cuales se ha estudiado la conformación de la molécula de atorvastatina amorfa en atorvastatina cristalina:

D1 : WO9703959 del 6 de Febrero de 1997. Folio(227-266)

D2 : WO9703958 del 6 de Febrero de 1997. Folio(267-280)

D3 : WO0136384 del 25 de Mayo del 2001. Folio(303-324)

En los documentos D1 y D2 del mismo solicitante, se refieren a formas cristalinas de atorvastatina conocida con el nombre de hemisal de calcio del ácido [R-(R*, R*)]-2-(4-fluorofenil)-β, δ-dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico designado como una forma I, forma II y forma IV en el D1 y la forma III en el D2, caracterizados por tener un patrón de difracción de rayos X en polvo y/o en estado sólido, así como los métodos para la preparación y la composición farmacéutica del mismo, que es útil como agentes para tratar la hiperlipidemia y la hipercolesterolemia.

Adicionalmente el opositor especifica que una forma cristalina representa un ordenamiento en el espacio o red cristalina de una estructura química (fenómeno denominado " **Polimorfismo**", y sólo se requiere conjugar unas condiciones apropiadas de cristalización para obtener un polimorfo derivado. Por lo tanto aún alterando la forma de la molécula de atorvastatina, los componentes de dicha molécula se mantienen iguales, alterándose únicamente algunas propiedades fisicoquímicas del producto.

Teniendo el conocimiento de D1 y D2 y el conocimiento de la técnica que dicta que las modificaciones polimórficas de un compuesto, en general pueden alterar algunas propiedades como velocidad de disolución, punto de fusión, difracción de rayos X, se puede deducir que las formas cristalinas denominadas, forma V, forma VI, forma VII, forma VIII, forma IX, forma X, forma XI, forma XII, forma XIII, forma XIV, forma XV, forma XVI, forma XVII, forma XVIII y forma XIX o un hidrato de las mismas se derivan del arte anterior y es obvio para cualquier persona versada en la materia.

Con respecto al documento D3 de Teva habla de formas cristalinas de atorvastatina denominada como forma V caracterizada por tener un patrón de difracción de rayos X en polvo y/o en estado sólido. Como se nota la solicitud colombiana hace referencia a la misma molécula de D3 en donde queda demostrado que los componentes de la molécula se mantienen iguales y sólo se alteran propiedades fisicoquímicas del producto. Por lo tanto este documento D3 afecta la novedad.

Por lo tanto, el opositor concluye que la solicitud de patente carece de novedad y altura inventiva a la fecha de prioridad 29 de Junio de 2001 ".

3.2. Respuesta de Warner – Lambert Company LLC a oposición de Procaps.

El solicitante alega diferir de las apreciaciones hechas por el oponente ya que se basan en un concepto erróneo de los criterios de novedad y nivel inventivo.

Para la novedad, una invención se considera nueva cuando no ha sido **divulgada** por una descripción escrita u oral, utilización o comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o , de la prioridad reconocida. Además esta divulgación debe ser detallada y suficiente para que una persona medianamente versada en el arte pueda reproducir perfectamente la invención.

Recalca nuevamente el objeto de la invención la cual consiste en describir nuevas formas cristalinas de la sal hemicálcica del ácido [R-(R*, R*)]-2-(4-fluorofenil)-β, δ-dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico, denominadas forma V, forma VI, forma VII, forma VIII, forma IX, forma X, forma XI, forma XII, forma XIII, forma XIV, forma XV, forma XVI, forma XVII, forma XVIII y forma XIX o un hidrato de los mismos, caracterizados por el patrón de difracción de rayos X en polvo.

El solicitante divulga que los compuestos que presentan estructuras amorfas, generalmente no son comercializados, debido a que son inestables tanto química como físicamente. El objetivo es establecer cuál polimorfo tiene las propiedades más apropiadas, tales como tamaño de partícula, velocidad de disolución, solubilidad, biodisponibilidad y estabilidad. Afirma que es imposible conocer a priori las formas cristalinas que pueda formar un compuesto químico en estado sólido, y de igual manera predecir que forma cristalina será estable y adecuada para su formulación.

Por todos estos argumentos el solicitante considera que ninguno de los documentos citados por el oponente anticipa de manera detallada y suficiente las formas cristalinas específicas reclamadas por la solicitud en trámite.

También expresa que el documento D3 del oponente divulga una "supuesta" nueva forma cristalina de sal de calcio de atorvastatina: Forma V; al analizar los difractogramas, tanto de la presente solicitud como del documento 3, claramente se puede observar que el difractograma de la presente solicitud presenta picos con alta resolución, por lo que concluye que esta forma presenta un empaquetamiento ordenado (forma cristalina); mientras que el difractograma expuesto en D3 presenta una baja resolución de picos, lo que indica un empaquetamiento desordenado, es decir es una forma amorfa.

Finalmente concluye que la presente invención presenta nuevas formas cristalinas de atorvastatina y como se demostrò, no existe coincidencia estructural, con lo divulgado en el estado de la técnica.

En cuanto al nivel inventivo el solicitante manifiesta que los documentos citados por el oponente, ni divulgan, ni sugieren, ya sea en forma individual o en combinación, las nuevas formas cristalinas de la presente invención y mucho menos sus beneficios. Es imposible para una persona medianamente versada en la materia determinar, a priori, que un nuevo polimorfo exista y mucho menos determinar con algún grado de certeza su estructura tridimensional exacta, sus propiedades fisicoquímicas y su actividad biológica. Algunos compuestos en estado sólido presentan una o más formas cristalinas, pero no existe un método conocido que pueda predecir las formas cristalinas que pueda presentar un compuesto en particular.

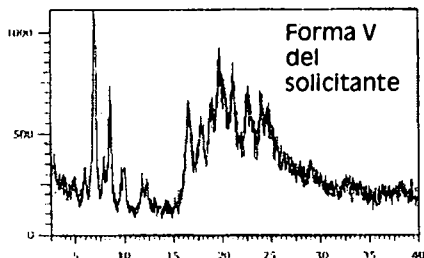
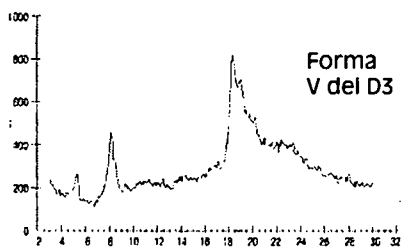
Para la forma cristalina VII, la cual toma como ejemplo; i) describe que tiene muy buena estabilidad química, comparable con la forma I, la cual le daría una vida media aumentada y una fecha de caducidad posterior. Reseña otras ventajas como ii) que se puede preparar de solventes no tóxicos, como es el sistema acetona/agua, mientras que la forma I se prepara en metanol / agua, iii) que contiene menos agua lo cual significa que esta forma contiene más moléculas de atorvastatina, es decir tiene más potencia y iv) que tiene mejores propiedades de tableteo.

Por este motivo, concluye que el resultado es sorprendentemente inesperado, lo cual de ninguna manera sería obvio para una persona medianamente versada en el arte, ni evidente a partir del estado del arte.

3.3. Respuesta del Examinador técnico de Fondo a oposición de Procaps y Warner – Lambert Company LLC.

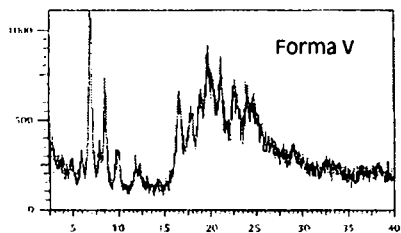
Para la evaluación de patentabilidad de la presente solicitud, se tuvieron en cuenta los documentos aportados por el opositor (D1 y D2), ya que dichos documentos los cuales desvirtúan el nivel inventivo.

El documento D3 no desvirtúa la novedad ya que, el difractograma obtenido por la presente solicitud para esta forma cristalina es diferente al de dicho documento, como se observa a continuación:

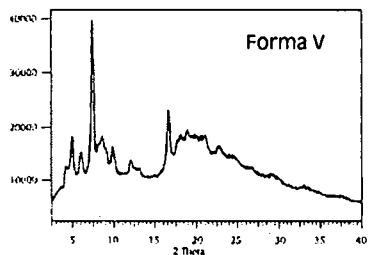


Adicionalmente al revisar la documentación correspondiente encontramos lo siguiente:

Los difractogramas tomados para la forma cristalina V en la presente solicitud son los siguientes :

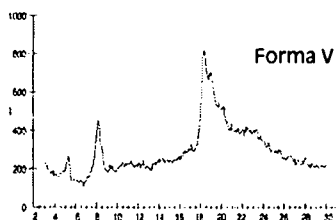


Difractograma obtenido
En un equipo Shimadzu XRD-6000



Difractograma obtenido
En un equipo Inel XRG-3000

Y el difractograma obtenido en D3 es el siguiente :



Difractograma obtenido en un equipo Philips X-ray power

Se observa que para la misma solicitud, en la forma cristalina V analizada , en dos equipos diferentes, los difractogramas obtenidos presentan características totalmente diferentes, por lo cual el solicitante no puede alegar que la forma cristalina V reseñada en el documento D3 es "supuesta" si dentro de sus mismas condiciones experimentales no se obtienen datos reproducibles para la misma forma cristalina.

El solicitante describe para la forma cristalina VII, las ventajas de estabilidad química, utilización de solventes menos tóxicos en su preparación, que contiene menos agua lo que aumenta su potencia y mejores propiedades de tableteo.

De acuerdo a este punto se le requiere anexar datos que permitan comparar las características de estabilidad de las formas cristalinas anteriores, con las de la presente solicitud.

3.4. Argumentos Tecnoquímicas S.A. y Lafrancol S.A.

El opositor documenta lo siguiente:

" La solicitud colombiana 03107810 carece de nivel inventivo, ya que frente a idénticas pretensiones de patentamiento de formas cristalinas de la sustancia atorvastatina, la superintendencia ha resuelto negar las solicitudes como :

Solicitud colombiana 96037513 y la solicitud 96037514, que se refieren a la forma cristalina III y formas cristalinas I, II y IV respectivamente de la atorvastatina, y luego de una sencilla comparación entre estos documentos y el de la presente solicitud en trámite carecen por completo de nivel inventivo, las 15 formas cristalinas reivindicadas, ya que las solicitudes negadas, revelaban la misma sustancia **ATORVASTATINA**, en las formas cristalinas I, II, III y IV y los hidratos de las mismas.

También especifica que a pesar de que las formas cristalinas de la presente solicitud no son las mismas, a las de las dos solicitudes que fueron negadas, no son más que manifestaciones cristalinas específicas de una molécula conocida en el estado de la técnica como es la sal cálcica de ATORVASTATINA.

El opositor también considera, que la caracterización de dichas formas cristalinas, dada por los patrones de difracción de rayos X en polvo, carece de nivel inventivo, pues es una técnica útil y rutinaria en la caracterización de formas cristalinas.

También el opositor considera que, la presente solicitud de patente de las 15 formas cristalinas de Atorvastatina carece de nivel inventivo, comparándola con los documentos de solicitudes colombianas 96014565 y 96014567, las cuales también fueron negadas en su momento y se encuentran también relacionadas con formas cristalinas pero en este caso del principio activo de la Olanzepina.

Adicionalmente, anexa una copia del estudio titulado "Polimorfismo y patentes" de Silvia Susana Giarcovich y también anexa el documento "Solicitudes de patentes sobre polimorfos en Colombia: Aspectos técnicos, legales y económicos" de Asinfar,

Por último concluye, que como se ha visto en reiteradas oportunidades, la superintendencia ha resuelto negar solicitudes de patentamiento de polimorfos de sustancias conocidas, máximo si se caracterizan por difracción de rayos X y estos no ofrecen ventajas inesperadas o fuera de lo común de la sustancia original o de otros polimorfos, queda demostrada la carencia de nivel inventivo de esta clase de solicitudes.

Posteriormente en una sustentación a la oposición realizada inicialmente, dicho complemento hace referencia a una solicitud de patente número 96064770 la cual habla sobre la forma cristalina monohidratada del CDCH – Moxifloxacina.

En este se hace referencia a que el fenómeno de polimorfismo está ampliamente distribuido en las sustancias de interés farmacéutico, que este fenómeno incluye estudios rigurosos en la preformulación, su grado de estabilidad, métodos de preparación y que es tarea del farmacéutico formulador realizar estudios profundos acerca del polimorfismo en los materiales que va a utilizar.

Por lo tanto concluye nuevamente que la solicitud carece de nivel inventivo, ya que normalmente una persona versada en la materia, las nuevas formas cristalinas de Atorvastatina son evidentes en el estado de la técnica.

El opositor anexa el documento "Crystalline solids" en esta sustentación."

3.5. Respuesta del Examinador técnico de Fondo a oposición de Tecnoquímicas y Lafrancol.

En cuanto al método de difracción de rayos X, se aclara que la evaluación de nivel inventivo se realiza para la forma cristalina reivindicada y no sobre el método analítico utilizado.

En cuanto los documentos patente referenciados en su oposición, se le informa que las decisiones tomadas sobre estos , no son siempre aplicables a otras solicitudes aunque estas parecieran similares.

Adicionalmente, la copia anexa del estudio titulado "Polimorfismo y patentes" de Silvia Susana Giarcovich, no fue tenido en cuenta, por no saber la fecha de publicación de este y también el documento "Solicitudes de patentes sobre polimorfos en Colombia:Aspectos técnicos , legales y económicos" de Asinfar, tampoco fue tenido en cuenta porque su fecha de publicación (Abril 9 de 2002). es posterior a la de la fecha de prioridad .

El opositor anexa el documento "Crystalline solids" , el cual no fue utilizado durante la evaluación, por no encontrar elementos relevantes para la evaluación de patentabilidad.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 29 de Junio de 2001, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

Nº	Documento	Título	Fecha de Publicación*
D1	WO9703959	Crystalline [R-(R*,R*)]- 2-(4-fluorophenyl)-Beta,Delta-Dihydroxy -5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (atorvastatin).	6 de Febrero de 1997.
D2	WO9703958	Form III Crystalline [R-(R*,R*)]- 2-(4-fluorophenyl)-Beta,Delta-Dihydroxy -5-(1-Methylethyl)-3-Phenyl-4-[(Phenylamino)Carbonyl]-1H-pyrrole-1-heptanoic acid hemicalcium salt (atorvastatin).	6 de Febrero de 1997.

5. Análisis de patentabilidad (según requisito) (artículo 14 D486)

Se aclara que para el presente análisis de patentabilidad el término : sal hemicálcica del ácido [R-(R*, R*)]-2-(4-fluorofenil)-β, δ-dihidroxi-5-(1-metiletil)-3-fenil-4-[(fenilamino)carbonil]-1H-pirrol-1-heptanoico hace referencia a la ATORVASTATINA

5.1. Nivel inventivo (artículo18 D486)

El documento del estado de la técnica más cercano es D1 (Folios 445-492) el cual enseña formas cristalinas de la atorvastatina forma I, II y IV, que es útil como agente hipolipidémico y/o hipocolesterolémico. La diferencia con D1 es que en esta solicitud las formas cristalinas de la atorvastatina o un hidrato de la misma, presentan un patrón de difracción de rayos X

(valores 2Φ medidos usando radiación CuKα) diferentes a la anterioridad, la cual comprende **formas cristalinas de la atorvastatina denominadas forma I, forma II, forma IV de atorvastatina o un hidrato de la misma.**

Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a las formas cristalinas reivindicadas en comparación con las formas cristalinas del Estado de la Técnica más cercano; porque **estas formas cristalinas siguen siendo útiles como agente hipolipidémico y/o hipocolesterolémico.**

Así que el Problema Técnico planteado en esta solicitud : la necesidad de formas cristalinas de atorvastatina, que garanticen una mejor estabilidad química, que se puedan preparar en solventes menos tóxicos, una mejor propiedad para el tableteo , una vida media aumentada y fecha de caducidad posterior , se había solucionado previamente mediante el desarrollo de formas cristalinas diferentes de la atorvastatina. De manera que las nuevas formas cristalinas **son una alternativa a los formas cristalinas conocidas** porque no presentan un mayor efecto como agente hipolipidémico y/o hipocolesterolémico.

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D1 y D2 (Folios 493-518), hubiera sugerido sin mucho esfuerzo de su parte crear distintas estructuras cristalinas basado en su experiencia modificando los parámetros de obtención de estas como : la naturaleza del disolvente , temperatura , velocidad de enfriamiento , agitación , cantidad de disolvente usado, pureza del disolvente, presión , evaporación , entre otros, con el fin de mejorar las diferentes propiedades fisicoquímicas las cuales están determinadas por la naturaleza del estado cristalino como : solubilidad (la cual provoca , cambios en la velocidad de disolución y en la biodisponibilidad), volumen molar, capacidad calorífica, conductividad, densidad; viscosidad, tensión superficial, difusibilidad, dureza del cristal, forma del cristal y color, y punto de fusión entre otras, para lograr las formas cristalinas reivindicadas que no parecen tener un mayor efecto como agente hipolipidémico y/o hipocolesterolémico.

Por lo cual se consideran obvios para el experto en la materia. En consecuencia, carecen de nivel inventivo.

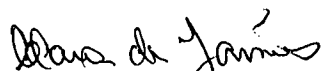
6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO9703959	1-15	Nivel Inventivo
D2	WO9703958	1-15	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



CLARA CECILIA CASTELLAMOS DE JAIMES
Jefe de División de Nuevas Creaciones(E)

El anterior requerimiento fue notificado por fijación en lista, de fecha

13 JUL. 2007

CONCEPTO TECNICO No. 963	EXAMINADOR TECNICO Código No.202075
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